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THE PATHOGENESIS OF THE UREMIC SYNDROME

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I. INTRODUCTION

Modern knowledge of the clinical picture produced by renal insufficiency dates from the brilliant observations of Richard Bright, who first described the disease which bears his name in 1827. He continued his clinical studies and postmortem investigations and a few years later (1836) wrote as follows:

> "The importance and extensive prevalence of that form of disease, which, after it has continued for some time, is attended by the peculiar changes in the structure of the kidney, now pretty generally known by the names of 'mottling,' 'white degeneration,' 'contraction,' or 'granulation,' impresses itself every year more and more deeply on my mind; and whether I turn to the wards of the hospital, or reflect on the experience of private practice, I find, on every side, such examples of its fatal progress and unrelenting ravages, as induce me to consider it amongst the most frequent as well as the most certain causes of death in some classes of the community, while it is of common occurrence in all. . . .
>
> "The first indications of the tendency to this disease is often haematuria, of a more or less decided character: this may originate from various causes, and yet may give evidence of the same tendency: scarlatina has apparently laid the foundation for the future mischief: exertion in childish plays has done the same; or it has sometimes appeared to be connected with suppressed catamenia. Intemperance seems its most usual source; and exposure to cold the most common cause of its development and aggravation. . . .
>
> "The history of this disease, and its symptoms, is nearly as follows:
>
> "A child, or an adult, is affected with scarlatina, or some other acute disease; or has indulged in the intemperate use of ardent spirits for a series of months or years: he is exposed to some casual cause or habitual source of suppressed perspiration: he finds the secretion of his urine greatly increased, or he discovers that it is tinged with blood; or, without having made any such observation, he awakes in the morning with his face swollen, or his ankles puffy, or his hands oedematous . . . already his urine contains a notable quantity of albumen: his pulse is full and hard, his skin dry, he has often headache, and sometimes a sense of weight or pain across the loins. Under treatment more or less active, or sometimes without any treatment, the more obvious and distressing of these symptoms disappear; the swelling, whether casual or constant, is no longer observed; the urine ceases to evince any admixture of red particles; and, according to the degree of importance which has been attached to these symptoms, they are gradually lost sight of, or are absolutely forgotten. Nevertheless, from time to

> time the countenance becomes bloated; the skin is dry; headaches occur with unusual frequency; or the calls to micturition disturb the night's repose. After a time, the healthy colour of the countenance fades; a sense of weakness or pain in the loins increases; headaches, often accompanied by vomiting, add greatly to the general want of comfort; and a sense of lassitude, or weariness, and of depression, gradually steal over the bodily and mental frame. Again the assistance of medicine is sought. If the nature of the disease is suspected, the urine is carefully tested; and found, in almost every trial, to contain albumen, while the quantity of urea is gradually diminishing. If, in the attempt to give relief to the oppression of the system, blood is drawn, it is often buffed, or the serum is milky and opaque; and nice analysis will frequently detect a great deficiency of albumen, and sometimes manifest indications of the presence of urea. . . .
>
> "Again the patient is restored to tolerable health; again he enters on his active duties: or he is perhaps, less fortunate;—the swelling increases, the urine becomes scanty, the powers of life seem to yield, the lungs become oedematous, and, in a state of asphyxia or coma, he sinks into the grave; or a sudden effusion of serum into the glottis closes the passages of the air, and brings on a more sudden dissolution. Should he, however, have resumed the avocations of life, he is usually subject to constant recurrence of his symptoms; or again, almost dismissing the recollection of his ailment, he is suddenly seized with an acute attack of pericarditis, or with a still more acute attack of peritonitis, which, without any renewed warning, deprives him, in eight and forty hours, of his life. Should he escape this danger likewise, other perils await him; his headaches have been observed to become more frequent; his stomach more deranged; his vision indistinct; his hearing depraved: he is suddenly seized with a convulsive fit, and becomes blind. He struggles through the attack; but again and again it returns; and before a day or week has elapsed, worn out by convulsions, or overwhelmed by coma, the painful history of his disease is closed."

While Bright was occupied in correlating the pathological processes in the kidney with the accompanying clinical picture, his contemporaries made the important discovery of the association of renal insufficiency with elevation of the blood urea. This was observed in dogs by Prevost and Dumas (1821) and in patients by Christison (1829).

As regards the symptom complex of uremia little advance was made beyond the ideas of Bright until comparatively recent years. Ascoli (1903) suggested that renal insufficiency produced two different syndromes, i.e., urinary poisoning, due to retention products, and "renal uremia," characterized by convulsions and due to the action of "nephrolysins" from damaged renal tissue. Widal and Javal (1903), believing that the latter condition was the result of chloride retention, separated uremia into the chloruremic and the azotemic types. The modern viewpoint dates from Volhard's (1918) classical division of the uremic syndrome into true and false uremia.

Volhard pointed out that there were three different symptom complexes, only one of which was dependent on renal insufficiency, although the other two often occurred in conjunction with it. He designated as *acute pseudouremia* a syndrome characterized by violent headache, convulsions, and signs of increased intracranial pressure, and ascribed these manifestations to edema of the brain. Since this symptom complex was often observed in patients with acute nephritis and subjects with eclampsia who had no elevation of the urea or of other nitrogenous substances of the blood, Volhard believed that they were not a result of renal insufficiency even though they usually occurred in patients with renal disorders.

The term *chronic pseudouremia* was applied by Volhard to manifestations of disturbed cerebral circulation occurring in persons with benign hypertension, malignant nephrosclerosis or chronic glomerulonephritis. Among the more important of such manifestations are attacks of unconsciousness, transient monoplegias, hemiplegia, paraesthesias and anaesthesias, Cheyne-Stokes respiration, aphasia, disordered psychic states and evanescent visual disturbances. All of these phenomena, although common in persons with renal insufficiency, are of frequent occurrence in subjects who display no retention of the urinary substances in the blood. Such disorders, Volhard contends, are not true uremic manifestations but are due to vasospastic episodes in the central nervous system.

Oppenheimer and Fishberg (1928) have likewise emphasized the lack of relationship between renal insufficiency and such vasospastic crises which they designate as *hypertensive encephalopathy*, a term which they feel includes also the eclamptic manifestations of Volhard's acute pseudouremia, which they believe to be primarily due to angiospasm rather than cerebral edema. It should be emphasized *that the term "uremia" as employed in this review designates only that symptom complex which occurs in conjunction with and as the result of* *the retention in the blood of urinary waste products* and does not refer to the clinical syndromes of pseudouremia and of hypertensive encephalopathy, which although of frequent appearance in nephritic patients, have been clearly demonstrated to be independent of renal insufficiency.

Furthermore, as this definition implies, the review is not concerned in detail with the syndrome of *pre-renal azotemia*, which, although resembling true uremia in both chemical and clinical aspects, depends on factors which may be operative in the absence of renal disease.

II. THE CLINICAL PICTURE OF UREMIA

Excellent discussions of the various manifestations of uremia may be found in the recent publications of Becher (1933) and of Fishberg (1935).[1] The former author mentions gastro-intestinal, respiratory, "nervous" and psychic types occurring in various combinations. In regard to general manifestations, cachexia, anemia, hypothermia, and the appearance of a yellowish grey discoloration of the face and hands are emphasized. Becher points out that the color of the skin resembles that of pernicious anemia but is not generalized, being more limited to the exposed portions of the body. Aside from its color the skin may display urea crystals and various eruptions which may be hemorrhagic, urticarial, vesicular, papular or eczemoid.

The mental state of uremic patients is usually characterized by apathy, listlessness and fatigability; a tendency to move slowly and speak softly is commonly observed; deep coma is rare and usually appears only a few hours before death. The patients doze but do not sleep. When aroused they answer intelligently.

As regards the nervous system, headache is one of the most common symptoms. Becher has, however, pointed out that the true uremic headache is rarely severe and is not paroxysmal. He believes that the existence of an intense headache in uremic patients is to be attributed not to the renal insufficiency but to the coexistence of cerebral edema or of hypertensive encephalopathy. In the early stages of uremia the tendon reflexes are often increased. Later with increasing apathy they diminish and may disappear. The occurrence of an extensor response to plantar stimulation is evidence for the coexistence of cerebral vascular disorders. Muscular twitchings are common. They differ from those of tetany in that positive Chvostek and Trousseau signs are not commonly observed except when alkalosis as the result of vomiting coexists. Laryngeal spasm is also absent. Convulsions, while common in eclampsia and in acute nephritis, are of rare occurrence in chronic uremia except as a terminal manifestation.

---

[1] In preparing this review we have drawn freely on the writings of these two authors who have critically analyzed most of the important work on the subject.

As regards the circulatory apparatus, the common abnormalities are angiospastic retinitis, hypertension, cardiac hypertrophy, congestive heart failure and pericarditis. Acute pulmonary edema frequently ushers in the fatal termination. At necropsy the hypertrophied left ventricle is often contracted and may fail to exhibit dilatation, even in the presence of marked congestion and edema of the lungs. None of these circulatory manifestations is constantly present, all being often absent in acute nephritis and occasionally absent in chronic cases. Except for the pericarditis, which is ordinarily observed only in persons with unquestionable renal insufficiency, these disturbances which are frequently seen in patients who have no retention in the blood of urinary waste products appear to be related to the commonly associated hypertension and not to uremia *per se*. Even in chronic glomerulonephritis, hypertension, cardiac enlargement and retinal changes may occasionally be absent.

The breathing usually becomes abnormal at some time in the course of uremia. Rapid respiration associated with dyspnea as well as paroxysmal attacks of cardiac asthma are clearly due to congestive heart failure rather than to the renal disease. Either cardiac or cerebral vascular disorders may cause Cheyne-Stokes breathing. Stertorous respiration is commonly dependent on coexisting intracranial disturbances rather than on renal insufficiency. The deep sighing respiration of uremic acidosis resembles that of diabetic coma and in the absence of cardiac complications is not attended by subjective dyspnea. Becher has pointed out that while the deep breathing of diabetic acidosis is ordinarily associated with true coma, the same respiratory disturbance in uremia occurs in patients who are stuporous but can be aroused.

Vomiting is the most important and frequent of the gastro-intestinal manifestations. It is often one of the earliest manifestations of uremia, as Salvesen (1934) has shown, and it may occur at a time when chemical analyses reveal only slight evidence of renal insufficiency. Coffee-ground vomitus may lead to suspicion of the existence of carcinoma of the stomach. Stomatitis, parotitis, singultus and colitis associated with bloody diarrhea are fairly frequent findings.

The foregoing description applies to the uremic syndrome as observed in man. Except for the rare cases in which the sole functioning kidney is removed by mistake and for certain subjects suffering from poisoning by mercuric chloride one rarely sees "pure" uncomplicated uremia in patients. On the medical wards uremia is usually accompanied by cardiac or cerebral disorders, while the surgical cases of uremia ordinarily suffer from infections and obstructions in the genito-urinary tract. Since these associated disorders play an important part in the production of the symptoms observed one can best study uncomplicated uremia in experimental animals rendered anuric by bilateral nephrectomy or by double ureteral ligation. Such studies were reported by Herter (1897) and more recently by Mason, Resnik, Minot, Rainey, Pilcher and Harrison (1936).

In dogs with complete anuria a characteristic sequence of events is observed. For convenience in description the clinical picture may be divided into several stages which may either succeed each other progressively or exist simultaneously.

The *asymptomatic stage* lasts for the first 24 to 36 hours. At this time the animal appears normal except for the weakness which can be attributed to the operative procedure.

The *apathetic stage* begins insidiously and usually about 30 to 36 hours after the operation. The animal displays no striking abnormalities and may continue to eat well but is somewhat listless.

The *stage of gastro-intestinal irritation* usually sets in about two days after the onset of anuria. Vomiting is commonly the earliest and the most striking manifestation. Infrequent on the second postoperative day, it soon becomes copious and, in some animals, almost continuous. This symptom is usually progressive until within a few hours of death when it may cease. Diarrhea is a less frequent and less striking symptom.

The *stage of increased nervous irritability* may be observed at one time or another in most animals but is not invariable. The most frequent manifestation is twitching, which involves various muscle groups and often resembles shivering. In some animals a generalized coarse tremor affects the extremities and to a lesser extent the head, neck and tongue. The muscular twitchings are usually a late symptom, setting in occasionally on the second postoperative day but more frequently on the third or fourth. Outspoken twitchings sometimes disappear as the condition of the animal becomes grave. In an occasional dog they again reappear. Evidence of psychic irritation is unusual but is occasionally noted. Excitement, growling, snapping and barking without provocation may be seen in dogs who have previously displayed a phlegmatic temperament.

Increase in blood pressure develops following ureteral ligation in most dogs, [Hartwich (1930), Harrison, et al. (1936)] and is sometimes striking. Following bilateral nephrectomy inconstant changes in blood pressure are noted. A slight rise is sometimes seen on the second or third postoperative day. More frequently the arterial pressure undergoes a marked decline.

The *stage of narcosis* eventually comes to dominate the picture in all anuric animals. This develops gradually from the slight apathy and listlessness which appear about 48 hours after operation to a final state of extreme asthenia, in which the animal is unable to walk or stand, and responds either not at all or very feebly to stimuli. This picture is most outspoken shortly before death on the fourth or fifth postoperative day. In well marked instances the pulse is feeble, the respirations are slow and occasionally stertorous and the blood pressure is markedly reduced.

Death usually occurs between 85 and 120 hours after the operation. Two general sequences of events may be observed. In those animals which have displayed the most profound depression and which have either escaped muscular twitchings entirely or have had them to a minimal degree, death is the result of progressive enfeeblement of the peripheral circulation with eventual respiratory failure. Other dogs which have continued to display muscular twitchings may exhibit involvement of larger and larger muscular units, the twitchings being followed by tremors, at first localized and then generalized, the tremors being succeeded by opisthotonos and finally by generalized clonic convulsions ushered in by a cry and followed by death. Even in the markedly depressed animals who display no evidence of increased neuromuscular irritability and are in a state resembling narcosis or light anesthesia, a sudden violent fatal convulsion is at times observed.

In observing these uremic animals one gains the impression that the nervous system is being subjected to two different and opposite influences, the one tending to stimulate it and the other to depress it. In some animals the irritative phenomena have the ascendency. In others the depressive manifestations are more outspoken. More frequently the same animal successively displays the one and then the other group of symptoms and not uncommonly, although paradoxically, the same dog may at a given time exhibit signs both of stimulation and depression of the nervous system. An adequate explanation for this paradox would seem to be an essential starting point toward the unravelling of the pathogenesis of the uremic symptom complex.

III. UNITARY THEORIES OF THE MECHANISM OF UREMIA

In view of the number and diversity of the symptoms displayed by patients with uremia it is rather surprising that most of the older authors looked for a single toxic substance.

Urea was proposed by Bright (1831) and by Christison (1829). The evidence in favor of this substance consists of its constant occurrence in increased amounts in body fluids and of the fact that extremely large doses may produce toxic symptoms [Herter (1897), Leiter (1921), Streicher (1928)]. Against this hypothesis are the considerations that symptoms resembling uremia are only produced by very large amounts of urea, and further, that no close correspondence exists in patients between the severity of the uremic manifestations and the height of the blood urea. Furthermore, as pointed out by Peters and Van Slyke (1931), the factor of dehydration has not been adequately controlled in the experiments in which urea has been administered and it seems probable that symptoms ascribed to urea may have been actually due to loss of water as the result of profuse diuresis. Bollman and Mann (1927) found that when excessive water loss was prevented by transplantation of the ureters into the intestines the blood urea could be raised to excessive heights without signs of intoxication. It seems clear that urea is not solely responsible for the uremic syndrome. However, the possibility and even probability remains that urea is one factor. Thus, Becher (1925) pointed out that bacterial action on the large amounts of urea which are present in the intestinal tract in uremic subjects results in the formation of ammonia, which he believes to be the most important factor in the production of stomatitis and other irritative processes in the gastrointestinal tract. Baur (1932) has recently shown that urea tends to increase cell permeability and thinks that its accumulation may favor the entrance of toxic substances into cells which would otherwise escape them. Other respects in which urea may play a rôle will be discussed later.

Landois (1886) and also Schottin (1853) proposed *creatinine* as the toxin in uremia. The former author produced convulsions in animals by applying this substance to the brain. However, Feltz and Ritter (1880) showed that large quantities of creatinine could be injected intravenously without the production of symptoms and similarly negative results from intracisternal administration have recently been reported by Resnik and Mason (1936).

Becher has rightly pointed out that Ascoli's theory of "*nephrolysins*," i.e., toxic substances formed in the kidneys, cannot be correct because typical uremia is produced by bilateral nephrectomy.

The theory of *acid intoxication* [Straub and Schlayer (1912)] can account for only part of the picture because severe and fatal uremia may occur in the absence of acidosis [Harrison and Perlzweig (1925)].

Foster (1915)(1921) differentiated between the convulsive and the asthenic types of uremia and from patients with the former type isolated a *toxic base* which when injected into guinea pigs caused muscular twitchings, rapid breathing, convulsions and death. However, it now seems clear, from the work of Volhard (1918) and of Becher (1933), that the syndrome which Foster called convulsive uremia is not always due to renal insufficiency but may be dependent rather on changes in the cerebral circulation and in the water balance in the brain. In spite of this fact we shall discuss in a later section, evidence which suggests that the substance described by Foster probably plays a part in the production of the uremic syndrome.

Edema of the brain, which was believed by Traube (1870) to be responsible for uremia, appears to be of importance in the production of Volhard's acute pseudouremia but not to be directly related to the manifestations of renal insufficiency. Widal's (1903) division of uremia into the azotemic and the chloruremic types corresponds in a general way to Volhard's true uremia and acute pseudouremia, the latter being a manifestation of cerebral edema.

Increase in the osmotic pressure of the blood was proposed as the cause of uremia by Koranyi (1897)(1898). Since he found no increase in the electrical conductivity of the serum he concluded that retention of non-electrolytes was responsible. However, as Fishberg (1935) has pointed out, the uremic syndrome may be well marked when there is only a slight increase in the osmotic pressure and hence such a change can scarcely be the chief cause of the syndrome under discussion.

Dehydration does not appear to be the primary cause of uremia but is a factor of considerable importance in many cases. A clinical picture resembling in some respects that of uremia has been produced by the intravenous injection of hypertonic salt solutions by Lindemann (1900) and by Andrews (1927). However, since some patients with typical uremia are free from evidences of dehydration this must be regarded as a secondary rather than a primary factor. *Increased destruction of body protein* was demonstrated by Bradford (1892), who observed loss of weight and elevated nitrogen excretion in dogs deprived of three-fourths of their renal tissue. Becher (1933) has suggested that this is brought about by the retention of proteolytic ferments and Mason and Evers (1936) have found that the proteolytic activity of the sera of uremic dogs against normal dog fibrin is much greater than that of normal dog sera. Further investigations of the enzymatic properties of the body fluids of patients with renal insufficiency would be of much interest.

Feltz and Ritter (1880) suggested that retention of *potassium* was responsible for the syndrome of uremia. Elevation of the blood potassium is not, however, a constant finding [Rabinowitch (1924)].

To summarize: The various theories which have attempted to explain the manifold symptoms of uremia on the basis of the retention of some single toxic compound are not supported by adequate proof. It is therefore necessary that we consider the more modern concept which holds that uremia is dependent on the accumulation of several substances rather than one poisonous product.

Granting that unrecognized compounds probably play an important rôle it still seems justifiable to attempt an evaluation of the significance of those factors which have been shown by recent work to be of importance in the production of the clinical phenomena.

IV. ALTERATIONS IN THE COMPOSITION OF THE BODY FLUIDS IN RELATION TO UREMIA

A. Disturbances in electrolytes

1. Acid-base balance and dehydration. The underlying causes of the dehydration and acidosis usually observed in uremia have been discussed in detail by Peters and Van Slyke (1931). Depletion of physiologically available alkali is hastened by several means. Failure of the ammonia-forming mechanism of the body and polyuria combine to sweep a large amount of chloride and base out of the organism. In addition, vomiting not only interferes with the ingestion of food but leads to a further loss of both sodium and chloride, for the vomitus, although frequently lacking in free hydrochloric acid, usually contains appreciable amounts of salt. The resulting deficit of base augments the reduction of bicarbonate and acidosis results from the retention of such anions as inorganic sulphate, phosphate and undefined organic acids. Although in severe uremia the retained inorganic phosphate and sulphate may contribute about equally to the bicarbonate deficit, Hoffman (1935) has shown that the very high values for inorganic sulphate reported by previous workers were probably due to certain errors in the methods used.

The concentration of organic acids (usually calculated as the difference, in milli-equivalents, between the total base and the sum of the anions [HCO_3], [Cl], [PO_4] and [SO_4]) may markedly rise in the terminal stages. This is brought about by the failure to excrete organic acids arising from the increased catabolism of tissue protein and fat due to starvation and to poor carbohydrate utilization.[2]

Although acidosis and dehydration usually accompany uremia they are by no means essential features of the symptom-complex. Indeed uremia frequently exists in the presence of a normal acid-base balance or even with alkalosis [Harrison and Perlzweig (1925)]. Bicarbonate and saline therapy, while temporarily relieving the base deficit, does not alter the uremia itself in any significant fashion. The deep, signing respirations occasionally seen, referable to acidosis, and the rapid wasting aggravated by dehydration seem to be the chief relationships of acid-base alterations to the uremic state.

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[2] Oefelein (1936) has recently emphasized again the diabetic nature of the glucose tolerance curves of patients with renal insufficiency and has suggested that the kidney is concerned in the humoral control of carbohydrate metabolism. Linder, Hiller and Van Slyke (1925) found similar intolerances to sugar in nephritics with nitrogen retention, however their studies of respiratory exchange indicated that the fault lay in some factor such as retarded glycogen formation rather than inhibition of carbohydrate combustion.

2. Chloride. Three different types of alteration of body chloride may occur in uremia: (1) In states of complete anuria, in certain cases of obstruction to the lower genito-urinary tract, or following salt therapy there may be increased chloride concentration in the body fluids. This condition is relatively exceptional and uremia is in most cases associated with chloride deficiency. (2) Dehydration may lead to diminution in total electrolyte without necessarily altering the concentration of chloride in the body fluids. (3) In most cases, there is a reduction in chloride concentration.

The importance of chloride deficit has been emphasized by a number of investigators, and the literature on this subject has been summarized by Peters and Van Slyke (1931). These authors point out that several factors are operative in the development of the hypochoremia of which vomiting is perhaps the most important. Polyuria, isosthenuria and diarrhea contribute to the steady drain on the chloride and base reserves of the organism. Atchley and Benedict (1927) studied the serum electrolytes of dogs after bilateral ureteral ligation and found that the diminution in both chloride and bicarbonate in this condition was almost exactly balanced by the increase in inorganic sulphate and phosphate.

A number of authors have studied the effects of chloride deficiency. Porges et al. (1923) (1932), Blum and his coworkers (1928-a) (1928-b) and also Meyer (1932) described somnolence, weakness, coma, hypotension, hypothermia, albuminuria and elevation of the non-protein nitrogen of the blood as the result of chloride deficiency. Haden and Orr (1924) produced a somewhat similar syndrome in dogs with hypochloremia as the result of intestinal obstruction. Glass (1932) has recently studied dogs subjected to chloride deprivation by the repeated administration of apomorphine, histamine and salyrgan. Eventually the blood chloride was reduced by approximately fifty per cent and the animals exhibited weakness, stupor and finally coma. The non-protein nitrogen content of the blood steadily increased, reaching levels as high as those usually seen in uremia. At necropsy cerebral edema was found. The kidneys displayed no lesions at autopsy and Glass concluded the increase in non-protein nitrogen was entirely of extra-renal origin as the result of the destruction of body protein. It is clear that a syndrome resembling that of renal insufficiency both in clinical and chemical aspects may arise from the overloading of the body with the end-products of protein metabolism in spite of functional integrity of the kidney. This condition which is ordinarily referred to as *pre-renal azotemia*, will develop more readily when the circulation to the kidneys is impaired in consequence of dehydration or peripheral circulatory failure.

It is important to remember that renal insufficiency and pre-renal azotemia, although initially distinct mechanisms, frequently coexist, the latter complicating the former when hypochloremia becomes profound. Under such conditions adequate salt therapy may, as Fishberg has pointed out, cause symptomatic improvement without affecting the functional capacity of the kidney.

3. Magnesium. Retention of magnesium in uremia has been observed by Becher and Hamann (1932), who observed slight increases in the serum levels and thought that this substance might be related to the depression of the nervous sytem and the terminal fall in blood pressure. Walker and Walker (1936) found that the serum magnesium may be increased to twice its normal value in severe renal insufficiency. On the other hand, Denis and Hobson (1923) have denied that magnesium is retained in a significant degree.

The suggestion that magnesium retention is related to nervous depression in uremia is not strengthened by the observations of Hirshfelder (1932-a) (1934-b), who found that although drowsiness in patients with severe renal insufficiency was accentuated by magnesium sulphate administration and that coma was readily produced in nephrectomized animals by this means, the levels of serum magnesium had to be elevated far beyond those found by other authors in the uremic patients not treated with magnesium salts. It is doubtful if magnesium retention in uremia, uncomplicated by magnesium therapy, is sufficient to account for any of the symptoms or signs of the syndrome.

4. Potassium. It has been shown by Rabinowitch (1924) that the serum potassium concentration may be elevated in severe renal insufficiency even though the total base is diminished, and these findings have been confirmed by others. No characteristic changes have been reported to take place in the cerebrospinal fluid if one excepts the curious results of Richter-Quittner (1922). [The literature on the composition of the spinal fluid in health and disease has been summarized by Katzenelbogen (1935).]

Resnik and coworkers (1936) have shown that relatively small amounts of potassium chloride administered intracisternally to dogs causes stertorous breathing, twitching and rise in blood pressure; however, the amounts employed were sufficient to raise the cerebrospinal fluid potassium concentration somewhat above that so far reported in any pathological state. Much larger amounts were given intravenously without appreciable effect. The available evidence, therefore, would permit potassium to be assigned at most only an augmentative and subsidiary rôle in the production of irritative phenomena in uremia.

5. Calcium and phosphorus. There is much evidence which suggests that some of the uremic manifestations are related to a diminution in the calcium ions in the blood. Thus, Marriott and Howland (1916) observed decline in the serum calcium in patients with renal insufficiency and this finding has been confirmed by numerous other observers. The deficiency of the plasma proteins, which is present in many patients, is evidently not the sole factor because patients may have a diminution in the calcium content of the serum even though the plasma proteins are normal [Peters and Van Slyke (1931)]. In such instances it has been assumed that the diminution in calcium took place at the expense of the ionized fraction and this has recently been shown to be the case by McLean and Leiter (1935), who, using the frog heart method of McLean and Hastings (1934), demonstrated a decrease in the ionized calcium of the serum of patients with uremia.

The accumulation of inorganic phosphate in uremic body fluids is an almost invariable finding and the predominance of evidence points toward this being responsible for the calcium ion deficit. In many instances, however, the rise in inorganic phosphate in the serum is insufficient to cause a large alteration in calcium ion concentration and in those cases certain organic anions such as oxalate and citrate may be augmenting the effects of inorganic phosphate. Becher (1933) believes oxalate retention to be the cause of the calcium ion deficiency. It is well known that oxalates and citrates arise from intermediary metabolic processes and oxalate crystals are commonly observed in urinary sediment.

In addition it is known that intravenous oxalate administration causes a fall in the serum calcium concentration and that the onset of motor irritative symptoms is related to the development of calcium ion deficit, the symptoms themselves closely resembling those seen in certain patients with uremia [Storti (1935)]. Although oxalate has been identified following its isolation from large quantities of blood, there is little agreement concerning the normal level of blood oxalate and the extent of its fluctuation in renal disease [Reinwein (1935)], and no relation was observed by Scaglioni (1935) between the degree of oxalemia and the clinical signs of uremia. The method most commonly employed for the determination of blood oxalate [Merz and Maugeri (1931)] is indirect and the values obtained in pathological states may be due in part to other organic acids, for example, succinic acid [Reinwein] which would not alter the calcium ion concentration.

Pucher, Sherman and Vickery (1936), using a specific method have confirmed the work of earlier investigators indicating that citrate is normally present in small quantities in blood of dogs but no satisfactory data are available concerning its behavior in patients with renal insufficiency.[3] The literature on citrate metabolism has been summarized by Sherman, Mendel and Smith (1936b).

At present it is not possible, therefore, to evaluate the rôle of either oxalate or citrate in respect to uremic hypocalcemia and in the absence of direct measurements of calcium ion concentrations, the concentration of inorganic phosphate still serves as the best index of impending or existing calcium ion deficit.

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[3] The citrate content of dogs blood may be increased to about five times the normal level by oral administration of citric acid without any untoward effects [Sherman, Mendel and Smith (1936b)].

In addition to the undoubted importance of phosphate, and the possible significance of oxalate and citrate there is suggestive evidence that guanidine retention may also be concerned in the physiological antagonism of calcium. This will be discussed later.

Although the possible significance of the retention of oxalate and of citrate-like substances in the production of calcium deficiency is as yet an open question, there is much evidence which indicates the important rôle (in this regard) of phosphate accumulation. DeWesselow (1923-a) (1923-b) (1924) found that the level of the blood phosphate was a more accurate prognostic guide in uremia than was the blood urea. He ascribed the muscular twitchings of uremia to phosphate retention. This view-point was strengthened by the previous experiments of Binger (1917), who had shown that the intravenous injection of alkaline or neutral sodium phosphate was followed by decline in the serum calcium and by the development of shivering, twitching, extensor rigidity and clonic spasmodic jerks.

It has been generally assumed that the increased neuromuscular irritability of uremia is of peripheral origin. However, the fact that carpopedal spasm and the signs of Chvostek and of Trousseau which are so frequently present in infantile tetany are usually absent in uremia, even when the twitchings are present, raises doubt as to whether the mechanism of the muscular movements is similar in the two conditions. (We are not aware of any investigations concerning the electrical reactions of the muscles of patients with uremia.) Recent studies by Mullin (1935) and by Resnik and his co-workers (1936) have shown that diminution in the calcium ions of the cerebrospinal fluid of dogs by the introduction into the cisterna magna of sufficient amounts of phosphate, oxalate or citrate regularly produces muscular twitchings, increase in blood pressure and stertorous breathing and sometimes causes periodic breathing, extensor rigidity and convulsions—a syndrome resembling that seen in certain patients with uremia. These observations raise the question as to whether the muscular movements of uremia may not be of central rather than peripheral origin. The experiments of Mason and his co-workers (1936) indicate that intravenous phosphate injections such as those described by Binger produce their effects by central rather than peripheral action. If the effects were of peripheral origin it would be difficult to explain the observed delayed onset.[4] These workers found, moreover, that the symptoms paralleled a rise in cerebrospinal fluid inorganic phosphate and a fall in the cerebrospinal fluid calcium ion concentration, these changes occurring at a considerable interval after the intravenous injection. Anesthesia tended to diminish the symptoms of neuromuscular irritability resulting from the injections. This may explain why some authors failed to observe twitchings following phosphate administration.

In general, one may say that many of the irritative phenomena which are observed in uremic patients can be reproduced by the intravenous injection of inorganic phosphate in experimental animals. However, the effects are profoundly influenced by the state of the animal as regards anesthesia, and appear to be related rather to an increase in the inorganic phosphate of the cerebrospinal fluid than to that in the blood, the symptoms being initiated by the resulting calcium ion deficiency.

Information pertaining more directly to the rôle of phosphate retention in uremia is available from observations made by Mason et al. (1936) on dogs following either bilateral nephrectomy or double ureteral ligation. Their chief findings may be summarized as follows: In animals so prepared the onset of motor irritative phenomena usually paralleled the rise in the inorganic phosphate and the decline in the ionized calcium of the cerebrospinal fluid rather than the corresponding changes in the blood. The motor irritative phenomena could be initiated at an earlier time by the administration of inorganic phosphate and could be inhibited by intracisternal injections of ionized calcium salts. It was emphasized, however, that some animals exhibited these symptoms in the absence of increase in the inorganic phosphate of the cerebrospinal fluid; and likewise certain dogs failed to display augmented neuromuscular irritability in spite of such increase. It was concluded that the presence or absence of muscular twitchings and similar manifestations were related not only to changes in calcium ion concentration but to at least two other factors, one acting similarly to calcium ion deficit, and the other inhibiting the consequences of such a deficit. Recent evidence indicates that there are certain organic compounds which accumulate in the uremic organism and exhibit such behavior.

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[4] Storti, who studied the effects of the intravenous administration of oxalate to rabbits likewise observed a delay in the development of the motor irritative phenomena.

B. Disturbances in organic metabolites

1. Phenols. The evidence which has been cited appears to indicate that a "central" calcium ion deficit is important in the production of the irritative phenomena of uremia. However, this cannot be the only factor for one may observe animals with a high spinal fluid inorganic phosphate without muscular twitchings. This fact raises the question as to whether there may not be some inhibiting agents. As has been mentioned the response of animals to injection of phosphate varies according to the type and depth of anesthesia. Substances having a narcotic action must be responsible for the apathy, weakness and comatose state often seen in uremia.

The obvious chemical relationship of urea to certain narcotics suggests that it may play a rôle in this regard. However, as Leiter (1921) has shown, the concentrations of urea required to produce a stuporous state are much greater than the concentrations ordinarily encountered in uremia and hence it is evident that urea cannot be the responsible agent.

Another group of chemical substances which have been held responsible for the depressed condition of the uremic patients is the free phenols. This point of view has been developed and advocated by Becher (1933), who has studied exhaustively the problem of uremia. He believes that the syndrome is dependent not on one but on many toxic substances, but ascribes the most significant rôle to phenols and other aromatic compounds which he has shown to accumulate in the blood of uremic patients.

The free phenols which include phenol, paracresol, indole and other related substances are formed in the body as the result of processes involving deamination, decarboxylation and oxidation of the aromatic amino acids: tyrosine, phenylalanine and tryptophane. There is some question as to whether free phenols are formed in the normal processes of intermediary metabolism; rather they appear to result mainly, if not entirely, from bacterial action on protein derivatives in the intestine. These substances are normally absorbed from the gastro-intestinal tract and are detoxified by conjugation with sulphuric or glycuronic acid. The adequateness of this detoxification depends on the functional integrity of the liver, intestine, and whatever other organs may be involved in the processes. The sites of these reactions have been discussed by Houssay [Houssay (1936)]. The conjugated phenols are relatively harmless in contrast to the highly toxic free phenols.

The chief evidence on which Becher bases his conception of the significance of phenols in uremia is as follows:

(1) In chronic nephritis the increase in phenols in the blood tends to parallel the severity of the uremic manifestations more closely than does that of the non-protein nitrogen [Becher (1933)].

(2) In acute nephritis patients may have marked nitrogen retention without uremic symptoms and in such cases the blood phenol concentrations are usually within normal limits.

(3) Chronic phenol intoxication produces a symptom-complex resembling in many respects that of uremia. [We also have recently observed a case illustrating this fact.]

(4) The introduction of aromatic amino acids into the rectum of persons with uremia increases the severity of the symptoms.

(5) The onset of uremic coma coincides with the appearance in the cerebrospinal fluid of free phenols.

(6) Phenol and phenol derivatives are themselves capable of producing and aggravating renal damage.

Becher's contention that uremia is ordinarily accompanied by increased concentrations of phenols in body fluids has been confirmed [Mason, et al. (1936)] both in clinical and in experimental uremia; however, the interpretation of such observations is complicated by the non-specificity of the methods for the determination of phenols. The Rakestraw (1923) method which was employed by the latter workers admittedly measures not only phenols but many related substances and the validity of the procedure employed by Becher has not yet been adequately demonstrated. However, granting the quantitative inaccuracies of such methods there is no reason to doubt their qualitative significance in indicating a general relationship between the symptoms of uremia and the retention of phenols.

That phenols are capable of causing stupor has been demonstrated by the study of experimental phenol intoxication. Recent investigations [Mason and co-workers (1936)] have shown that the administration of free phenols to dogs and to mice produces a state characterized at first by tremor, ataxia and salivation and shortly followed by weakness, apathy and stupor. Animals receiving doses which were not immediately fatal displayed well marked renal damage, particularly tubular degeneration. Somewhat similar clinical pictures and pathological findings have been described in man as the result of phenol intoxication. Whether in patients with nephritis phenol retention is sufficiently marked to produce further renal damage is an interesting but unsettled problem.

Another rôle of phenols in uremia was suggested by the observations of Mason, et al. (1936), who observed that the irritative phenomena—twitchings, rigidity, convulsive movements, stertorous breathing and increase in blood pressure—which are ordinarily initiated by the intracisternal administration of inorganic phosphate can be prevented by the previous administration of free phenols, either intravenously or intracisternally. This observation was interpreted as indicating that the occasional absence in clinical and experimental uremia of increased neuromuscular irritability in spite of the coincident existence of calcium ion deficit might well be accounted for by a rise in the concentration of free phenols in body fluids.

The deleterious effects of accumulated phenols may conceivably arise from the conjugated as well as from the free phenols. In the study already quoted it was found that the sulphate ester of paracresol was in itself somewhat toxic to dogs and to mice. Experiments designed to determine whether or not the accumulation of conjugated phenols impeded the further detoxification of free phenols were equivocal.

To summarize: The body fluids of the uremic organism exhibit increased concentrations of phenolic substances. However, the evidence for the importance of these compounds in the production of any parts of the uremic symptom-complex rests chiefly on inferences drawn from the study of experimental intoxication produced by them. Animals so poisoned present symptoms of depression such as those occurring in the uremic state. The irritative phenomena ordinarily produced by "central" calcium ion deficit as the result of the intracisternal administration of inorganic phosphate can be prevented by the previous administration of free phenols. This pharmacologic antagonism explains the absence in certain uremic subjects of irritative phenomena in spite of calcium ion deficit. The clinical picture of uremia is apparently related to a balance between two opposing mechanisms; on the one hand phenol accumulation—tending to produce weakness, stupor and coma, i.e., manifestations of depression; on the other hand calcium ion deficit—tending to produce twitchings, stertorous breathing, increase in blood pressure and convulsions, i.e., the manifestations of stimulation.

2. Guanidine. The foregoing statement regarding the balance of factors in the uremic symptom-complex should not be too broadly interpreted. Although accumulation of inorganic phosphate favors the establishment of calcium ion deficit and the onset of irritative manifestations while retention of "phenols" tends to produce depression, these are not necessarily the only substances concerned in this balance. Salvesen (1931) and also Peters (1932) have reported uremic patients with muscular twitchings and without phosphate retention. Mason, et al. (1936) observed similar conditions in an occasional dog with experimental uremia. It has already been mentioned that oxalate may be involved, and there is rather convincing evidence that guanidine and/or its derivatives may play a significant rôle.

Myers and Fine (1914) suggested that creatinine retention might be etiologically important in uremia because of the toxic guanidine group present in that compound. Foster (1915), the following year, reported the isolation of a poisonous organic base from the serum of patients with the "epileptiform type" or uremia. This substance, obtained by filtration of the serum through a semi-permeable membrane, was alcohol-soluble and was precipitable as the gold or platinum salt. The amount obtained from 200 cubic centimeters of blood when injected into a guinea pig caused twitchings, rapid breathing, convulsions and death. Foster made no claims concerning the identity of this substance, but from its chemical behavior and pharmacological effects it seems probable that it was guanidine or a guanidine derivative.

Evaluation of the rôle of guanidine in various pathological states has been complicated by the lack of methods which are specific for that base itself. It is freely admitted that the usual colorimetric methods yield color not only with guanidine but with related substances which may or may not have pharmacologic properties similar to it. For example, urea contributes slightly to the "guanidine"[5] color, although fortunately a correction for this is readily made.

Major and Weber (1927) again aroused interest in guanidine when they showed that the compound injected into animals produced a marked rise in blood pressure and that "guanidine" was present in increased concentration in the blood of certain patients with hypertension. The highest values were found in subjects with uremia. These observations were confirmed by Pfiffner and Meyers (1926). The same authors later (1930) improved their method and observed slight increases in some of their subjects with hypertension but without renal insufficiency. DeWesselow and Griffiths (1932) reported increased "guanidine" content in the blood of 9 of 23 patients with essential hypertension and in 2 of 8 subjects with varying degrees of renal insufficiency. Bohn and Schlapp (1932) found no increase in "guanidine" in persons with "red hypertension" but a definite rise in 10 of 13 persons with "pale hypertension" of which only 6 exhibited nitrogen retention, and the authors concluded there was no necessary relationship between renal insufficiency and increase in "guanidine" in the blood. Kleeberg and Schlapp (1930) found that most of their patients with hypertension and high blood "guanidine" values also had nitrogen retention and that some persons with renal insufficiency exhibited an increase in "guanidine" and a normal blood pressure. Recently it has been shown [Mason, et al. (1936)] that dogs with experimental anuria regularly exhibit a definite increase in the blood "guanidine" and that as the uremic symptoms increased in severity "guanidine" made its appearance in the cerebrospinal fluid.

The contradictory results which have been cited are probably due to differences in methods employed by the various investigators. Furthermore, the relationship of "guanidine" to blood pressure is no simple matter; for example, Lange (1933) has recently described a powerful depressor substance which appears to be a guanidine derivative since it gives the Sakaguchi reaction. The action of guanidine on blood pressure varies according to the method of administration, the anesthetic employed, and the duration of the experiment.

That guanidine may produce muscular twitchings has been recognized since the work of Paton (1916) (1925), and this work has been confirmed by Minot and Cutler (1928) (1929), who administered the compound subcutaneously, and by Resnik and Mason (1936) who injected it intracisternally. The latter authors observed rise in blood pressure, and respiratory stimulation in addition to muscular twitchings, and commented on the similarity of the state of the animals to that of certain patients with uremia.

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[5] As used here and throughout the remainder of this review the expression "*guanidine*" refers to the substance or substances responsible for the color reaction alleged to be due to guanidine, while the unqualified term *guanidine* refers to the base itself.

With chronic guanidine intoxication a somewhat different picture is produced. This has been described in detail by Minot and her coworkers [Minot and Cutler (1928) (1929); Minot and Dodd (1933)]. Following repeated subcutaneous injections a preliminary stage of excitement associated with muscular twitchings and increase in blood pressure is followed by pronounced depression with weakness, apathy, coma and hypotension. Copious vomiting usually occurs, diarrhea is common and autopsy reveals extensive acute gastroenteritis.

Recent observations by Minot (1936) indicate that the circulatory failure occurring in the later stages of guanidine intoxication is dependent on loss of fluid through damaged capillary walls with consequent decline in blood volume, diminution in cardiac output and fall in blood pressure. Although it seems certain that gaunidine acts antagonistically toward calcium ions *in vivo*, the mechanism of this behavior is not yet clear.

The evidence for the significance of guanidine in the pathogenesis of uremia is suggestive but not conclusive. Since the effects of this compound on blood pressure are variable under different conditions its importance in this regard cannot be evaluated at present. The interpretation of its rôle in the production of increased neuromuscular irritability is complicated by the fact that individuals may exhibit "hyperguanidinemia" in the absence of such manifestations. Whether or not this is due to antagonistic substances is still uncertain. However, there are instances in which motor hyper-excitability which can be produced by the administration of guanidine is present, and in which "guanidine" retention is the only demonstrable feature which could account for such symptoms.

If guanidine does play a rôle in uremia it is probably of especial importance in relation to gastro-intestinal disturbances. Vomiting is an outstanding manifestation of guanidine poisoning which may also cause diarrhea and hemorrhage into the gastro-intestinal tract. Furthermore, these manifestations are not commonly associated with states of calcium ion deficit or of phenol retention. Therefore, of the several disorders thus far considered, "guanidine" accumulation is the only one which appears to be in any way related to the uremic disturbances of the alimentary tract.

It should be emphasized that the evaluation of the rôle of guanidine in uremia is hindered, firstly, by the inadequacies of the methods for determining it; and secondly, by the presence in the uremic organism of substances which may augment or antagonize its admittedly complex action.

3. Urea. On the basis of his own observation that the amount of urea in the urine was diminished in patients with renal insufficiency, and of Christison's work (1829), which showed that large quantities of urea were present in the blood of such patients, Bright suggested that this substance might be concerned in the production of the clinical manifestations of renal insufficiency. The studies of Herter (1897), Leiter (1921), Streicher (1928), and of Hewlett, Gilbert and Wickett (1916), seemed to indicate that urea is definitely toxic when given in sufficient quantities. However, in order to produce intoxication it is usually necessary to raise the blood urea to a level considerably above that found in uremia. Furthermore, in patients with renal insufficiency little correspondence exists between the height of the blood urea and the severity of the uremic manifestations. In this respect it is interesting to note that the normal levels in the blood of elasmobranchs is of the order of 800 to 1000 milligrams per cent. The weight of evidence is therefore rather strongly against the concept that urea is the chief factor in the production of the uremic picture.

The suggestion of Frerichs (1851) that urea was indirectly toxic through transformation into ammonium carbonate, has been generally regarded as invalid in view of the lack of any considerable rise in the ammonia content of the blood in uremic states. However, Becher, who has pointed out that bacteria capable of transforming the urea into ammonia exist in the mouth and in the gastro-intestinal tract, believes that the ammonia so formed is of importance in the production of stomatitis, gastritis and colitis. This conception has recently received support from the work of Hessel and Pekelis (1933), who studied the material obtained from gastric fistulae in nephrectomized dogs. They found high values for the several non-protein nitrogen constituents, and observed that animals in which the gastro-intestinal secretions were removed displayed considerably less damage to the gastro-intestinal tract than occurred in control nephrectomized animals without fistulae. In some of their animals the concentration of ammonia in the gastric juice was as high as 200 to 300 milligrams per cent.

Another idea concerning the rôle of urea has been advanced by Baur (1932). This author found that rabbits given both trypan blue and urea developed much more diffuse staining of the cells than other animals given the dye alone. He showed that the absorption of dye from the gastro-intestinal tract was increased by urea, and that this compound hastened the onset and increased the severity of strychnine poisoning in experimental animals. He also found that the rate of passage of dyes into the cerebrospinal fluid could be increased by administration of urea. Baur concluded that urea has a general effect in increasing penetration into the body cells and believed that thereby it may cause relatively nontoxic compounds to become toxic. However, this concept was not supported by experiments carried out by Resnik and Rainey (1935), for these authors found that the minimum lethal doses for mice of paracresol and of guanidine were not significantly altered when urea was administered at the same time in doses of two grams per kilogram of body weight. The negative results of these workers cannot be regarded as entirely conclusive, however, for their experiments were of short duration and it is conceivable that similar investigations carried out on animals with more chronic intoxication might have yielded different results.

The suggestion has been made by Fishberg (1935) and also by Becher (1933), that the retention of excretory products in the blood may interfere with the detoxifying mechanisms of the body and thereby lead to accumulation of substances which normally occur only in traces. (Thus, if A, a nontoxic substance present in the food, is converted in the body to B, a toxic substance, which is further changed to C, which is another innocuous compound and a normal urinary constituent, it would seem to follow from the law of mass action, that the retention of C would be followed by a diminution in the rate of disappearance of B, with a rise in its concentration in the body fluids.) This suggestion was tested by Mason and his coworkers (1936). A group of dogs was given similar doses of guanidine, one-half of the animals having just previously received urea intravenously. The rate of disappearance of the guanidine from the blood was then investigated. These experiments showed quite definitely that the previous injection of urea caused a definite delay in the disappearance of the guanidine from the blood. *It appears that urea, while of itself a relatively innocuous substance, may be indirectly toxic by favoring the accumulation in the body of poisonous products of intermediary metabolism.*

Whether the same general principle which seems to apply to urea and guanidine also holds true for other metabolic processes is unknown. Investigations by Resnik and Rainey (1935) on the effect of the administration of conjugated phenols on the rate of disappearance of injected free phenols led to inconclusive results. Further studies on the relation between the accumulation of urinary waste products and the detoxification of their poisonous precursors are needed.

C. Accumulation of unknown toxic substances

Most of the manifestations of renal insufficiency can be accounted for by the accumulation in the body of the compounds which have been discussed. However, it seems very probable that other agents, as yet unknown, may also play a rôle. It was found, for example, by Mason et al. (1936) that the serum of dogs in an advanced state of uremia was highly toxic to the heart of the frog, producing ventricular systolic arrest, which sometimes endured for as long as twenty-four hours during which the auricle continued to beat. Since the effect came on rapidly with uremic sera and was produced only rarely by normal sera, and then only after prolonged contact with the frog's heart, it appears that the concentration of this agent was increased under the conditions of renal insufficiency. The substance responsible for this effect was found to be highly unstable and nondialysable.

The rôle, if any, of this compound having a digitalis-like effect in the pathogenesis of uremia is uncertain. Feil and Steuer (1929) found that the amount of digitalis needed to produce clinical and electrocardiographic effects was not altered in persons with uremia. On the other hand, Fishberg (1935) mentions two patients with renal insufficiency who developed digitalis intoxication from relatively small doses of the drug, while Kohn and Castopanagiotis (1933) found that in cats with experimental uremia the minimal lethal dose of digitalis was twenty-five to thirty per cent less than in normal animals. Conceivably this substance, which has such a striking effect on the frog's ventricle, may be related to the fact that the left ventricle of patients dying of renal insufficiency is usually found at postmortem examination to be firmly contracted, but no conclusion can be drawn until further data are available.

Certain aromatic amines have also been considered as of possible significance in uremia [Becher (1927), Chrometzka (1929)], but their rôle is not as yet clear.

Chrometzka (1929) has shown that uremic serum contains substances which, when concentrated by appropriate means, and injected into mice and rabbits, cause paralysis and death. The nature of this material is undetermined, but it apparently is not responsible for the diazo reaction given by such serum, which Chrometzka thinks is due to a compound having the properties of an aromatic alkyl amine.

It seems likely that a host of obscure metabolites accumulate in the body fluids of the uremic organism, but until more is known of the specific pharmacological action of each, it will be impossible to assign them any tangible pathogenetic rôle.

D. Changes in the composition of the cerebrospinal fluid

Several authors, impressed by the predominance of the disturbances in the nervous system in uremia, have believed that alterations in the composition of the cerebrospinal fluid were of especial significance. v. Monakow (1923) thought that the immediate cause of uremic coma lay in toxic alterations of the choroid plexus which allowed substances which had accumulated in the blood to escape into the cerebrospinal fluid. Becher (1935) claimed that the onset of coma usually occurred when free phenols appeared in the *liquor spinalis.* Mason et al. (1936) found that "guanidine," while absent from the cisternal fluid of normal dogs, could be found in measurable amounts in this liquid obtained from animals with advanced renal insufficiency. Resnik and his coworkers (1936-a) (1936-b) had previously shown that irritative manifestations closely resembling those of uremia could be produced by the intracisternal administration of either inorganic phosphate or of guanidine in doses which were entirely ineffective when injected intravenously. These authors concluded that central rather than peripheral calcium ion deficit was of chief importance in the production of the muscular twitchings and allied phenomena.

During states of progressive renal insufficiency the alterations in the blood may antedate those in the cerebrospinal fluid by a considerable period. Thus Mason and his coworkers (1936) found in their study of anuric dogs that depletion of bicarbonate and fall in pH in the blood occurred several days before similar changes could be observed in the cerebrospinal fluid. These observations were similar to those of Ptaszek (1927) who studied nephrectomized dogs. On the other hand Savy and Thiers (1929), investigating the alkaline reserve of patients with uremia, found that the carbon dioxide combining power was usually diminished more in the cerebrospinal fluid than in the blood. These various findings can perhaps be ascribed to differences in the chronicity of the disease processes, but it is difficult to understand the findings of Savy and Thiers.

Aside from changes in its composition, alterations in the pressure of the cerebrospinal fluid may be important in persons with renal insufficiency, and particularly in the production of vomiting, headache, papilledema and convulsions. Increased intracranial pressure is commonly observed in persons with cerebral edema (Volhard's acute pseudouremia) and does not appear to be directly dependent on retention products.

E. The rôle of disordered liver function

Certain facts suggest that hepatic dysfunction may play a part in the production of some of the manifestations of the symptom complex of advanced renal insufficiency. Among these are:

(1) In spite of the difficulties involved in the methods for the determination of indol, it seems to be established that free indol accumulates in the blood in significant concentration in the terminal stages of renal disease [Becker (1933)]. It is unlikely that this would occur if the liver were performing its functions of detoxification in a normal manner.

(2) There is a rather striking resemblance between certain depres-

sive symptoms of uremia and the clinical picture observed in severe hepatic insufficiency (cholemia).

(3) DeFlora (1932) found that the rate of disappearance of injected amino acids from the blood of dogs was markedly diminished by ureteral ligation. If one concedes, as is generally believed, that deamination is largely a function of the liver, his experiments indicate distinct hepatic impairment; however recent evidence [Krebs (1935)] indicates that the kidney participates to an important degree in the deaminative process.

The present evidence, admittedly incomplete, suggests that physiologic defense against those toxic substances which may arise in the body involves two mechanisms: detoxification by the liver,[6] and excretion by the kidney. (Of course the liver also has an excretory rôle *via* the bile, and the kidney is concerned in detoxification in certain instances.) Profound failure of either mechanism may well influence the other adversely; thus nephritis has been described as consequent upon advanced liver failure (hepatonephritis of Richardieu) and the evidence pointing toward the development of hepatic insufficiency in the terminal stages of renal disease has already been cited. Impairments of both of these organs will obviously be aggravated by the congestion resulting from the frequently coexisting heart failure.

V. THE MECHANISM OF SOME OF THE CLINICAL MANIFESTATIONS OF UREMIA

1. Coma. The extensive investigations of Becher (1933) point to the conclusion that the most important factor in the production of mental and physical apathy, weakness, stupor and coma in persons with renal insufficiency is the accumulation in body fluids of aromatic phenol derivatives. Studies on uremic dogs and observations on both experimental and clinical phenol intoxication which have been cited are in general agreement with this conclusion. There is also ample evidence which indicates that chloride deficiency, although not of invariable occurrence, may be of importance in the production of the depressed phenomena in certain patients. The available evidence does not indicate that magnesium excess is of any great importance except when brought about by excessive magnesium sulfate purgation. Whether in the absence of such treatment the accumulation of magnesium is of any significance will have to be decided by future work.

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[6] The classic concept of the exclusive rôle of the liver in detoxication is no longer tenable and other organs are now known to be the sites of certain conjugation reactions formerly thought to take place only in hepatic tissue. Thus phenol is apparently detoxified in the intestine although indol is converted to indoxyl almost entirely in the liver.

2. *Increase in neuromuscular irritability.* The observations which have been mentioned indicate that diminution in the ionized calcium of body fluids as the result of accumulation of substances forming unionized calcium salts is an important cause of muscular twitchings. This action is mainly if not entirely central and is related to the accumulation of these substances in the cerebrospinal fluid rather than in the blood serum. Retention of these anions does not appear to be the sole cause of muscular twitchings, which may also be dependent on the presence of excessive amounts of guanidine or some related substance. The present evidence, although not entirely conclusive, suggests that the guanidine also acts centrally rather than peripherally. The rôle of potassium retention is still uncertain and although salts of this element may cause marked twitchings when administered intracisternally, it has not yet been demonstrated that potassium accumulates in the body in sufficient amount to play a rôle in the production of irritative manifestations of uremia. The suggestion that oxalate is of importance still lacks confirmation from analysis of the body fluids. The absence of twitching in spite of calcium ion deficit can best be accounted for by the retention of substances such as the free phenols which have a narcotic action.

3. *Disturbances of respiration.* Rapid breathing, cardiac asthama and acute pulmonary edema are common complications of uremia but are due to failure of the left side of the heart and consequent pulmonary congestion (Harrison, 1935) and are not directly related to renal insufficiency.

Slow deep breathing simulating that of diabetic coma is less commonly observed and can be ascribed to acidosis.

Stertorous breathing and periodic respiration, when occurring in uremic patients, are likely to be dependent on associated cerebral vascular disease rather than on disturbances of kidney function.

However, since both of these disorders are sometimes observed in experimental animals following the administration of inorganic phosphate it is possible that phosphate retention may be in some cases one of the factors concerned. Iversen (1921) noted augmented breathing following the administration of inorganic phosphate to experimental animals. One of the most frequent causes of periodic breathing, when occurring in uremic patients, is congestive heart failure. Under such conditions the respiratory disturbance is related chiefly to two factors—the loss of carbon dioxide from the blood as result of hyperventilation, and sudden depression of the respiratory center at the onset of sleep [Harrison, et al. (1934)].

4. Circulatory disorders. Pericarditis has not been observed in animals with experimental anuria. This is not surprising in view of the short duration of the uremic state for this complication is much more common in chronic than in acute nephritis in patients, and the time factor is evidently of considerable importance in its production. Mason et al. (1936) found a serofibrinous effusion in the pericardial cavity of a dog within a few hours after the intravenous administration of large amounts of neutral sodium phosphate. This observation suggests that phosphate retention, which is an almost invariable accompaniment of chronic uremia, may play a rôle in the production of pericardial irritation. No definite conclusions can be drawn from a single experiment however, and it is likely that other factors are concerned.

The mechanism of the changes in blood pressure occurring in experimental uremia was studied by Harrison, Mason, Resnik and Rainey (1936). Their chief conclusions may be summarized as follows: Certain retention products such as inorganic phosphate tend to produce a rise in blood pressure. Other retention products such as "phenol" tend to have the reverse effect. Judging from the results of experimental guanidine intoxication "guanidine" retention may affect blood pressure in either direction. Dehydration as the result of excessive vomiting or copious diarrhea may also lower the blood pressure. The result is that bilaterally nephrectomized animals may display a slight increase, a well marked decrease, or no change in blood pressure.

Following ligation of both ureters the factors just mentioned are also operative. Here, however, chemical changes initiated by the damaged renal tissue and leading to a rise in blood pressure play the dominant rôle, so that most of the animals exhibit a distinct hypertension as compared to the preoperative state.

The observations which have been cited indicate that a slight rise in blood pressure occurring in uremic subjects may be accounted for by changes in the electrolyte pattern of the cerebrospinal fluid as the result of retention products. However, neither this mechanism nor other processes dependent on deficient renal excretion can be responsible for the marked rise in blood pressure which is usually found in persons with chronic nephritis because: (a) This increase in blood pressure usually precedes renal insufficiency. (b) Goldblatt and his coworkers (1934) have shown that impairment of the circulation to the kidney by partial obstruction to the renal arteries may cause a pronounced rise in blood pressure without severe impairment of renal function, and their results have been confirmed by Page (1935). (c) In anuric dogs a marked hypertension occurs only when abnormally functioning renal tissue is present in the body and extreme retention of waste products in nephrectomized animals results at most in relatively slight increase in blood pressure. "Renal hypertension" is evidently dependent on some factor other than the failure to excrete waste products.

5. Vomiting. This symptom, like the others discussed, appears to be based on a complex mechanism. In patients with acute and subacute nephritis who exhibit papilledema, vomiting may be due to increased intracranial pressure as the result of cerebral edema, for it may occur without renal insufficiency and may be benefited by measures which reduce the intracranial pressure. This mechanism possibly accounts for the observations of Salvesen (1934), who found that in certain patients vomiting occurred without any alteration in the ionic pattern of the blood and with only a slight elevation of urea. Becher (1933) has pointed out that in cases of this type the vomiting is apt to be violent but intermittent, while in patients with true uremia (as distinguished from cerebral edema of acute pseudouremia) the vomiting is less severe but more persistent.

Frequently emesis may be a prominent symptom in patients who display no evidence of increase in intracranial pressure. Here retention products appear to be responsible. Becher (1925) ascribed the dominant rôle to ammonium salts formed by bacterial action in the gastro-intestinal tract from the large amounts of urea present in the secretions. His contention is supported by the observations of Hessel and Pekelis (1933), who found values as high as 200 milligrams per cent for the ammonia content of the intestinal secretions of nephrectomized dogs with jejunal fistulae. They also observed that the intestinal mucous membrane above the fistula was more damaged than that below it, indicating that removal of the secretion tended to protect the mucosa. Since it is well known that ammonium salts administered by mouth frequently cause vomiting it seems likely that these substances which are formed in the gastro-intestinal tract in excessive amounts when the blood urea is elevated are of importance in this respect.

In chronic guanidine intoxication vomiting is pronounced. Since severe uremia, both in animals and in man, is usually associated with a well marked "hyperguanidinemia," it appears that retention of this substance probably plays a rôle in the production of vomiting. Here again one is confronted with the difficulty that the method used to measure guanidine is not highly specific and that a final interpretation of the significance of this substance in relation to vomiting as well as to the other symptoms cannot be made at the present time.

It appears, then, from the present evidence that the vomiting of uremia may be dependent on increased intracranial pressure, ammoniacal fermentation in the gastro-intestinal tract, "guanidine" retention, and quite probably on other factors as yet unknown. Regardless of its cause, copious vomiting has untoward effects on the organism. Its significance in the development of dehydration is obvious. Although copious vomiting may in exceptional instances produce alkalosis in uremic patients [Harrison and Perlzweig (1925)], and may more commonly tend to limit the severity of acidosis, this effect is less important than has been generally realized, for free hydrochloric is usually absent from the vomitus of persons with renal insufficiency [Peters and Van Slyke (1931)]. On the other hand the loss of chloride even though balanced by loss of base is not a matter of indifference to the organism, for, as has already been mentioned, the experimental studies of Haden and Orr (1923), Glass (1932) and Meyer (1932), and the clinical observations of Blum (1928) and of Porges (1932) have clearly shown that severe chloride deprivation leads to increased destruction of body protein and to a syndrome characterized by weakness, coma and elevation of the nonprotein nitrogen of the blood. A vicious cycle is thereby inaugurated, the vomiting, itself a result of renal insufficiency, tending to increase the available nitrogen for excretion and thereby to aggravate the existing uremia. A symptom initially compensatory in nature, aiding in the excretion of poisonous products retained by the damaged kidneys and serving to rid the body of substances irritating to the gastro-intestinal mucosa may therefore exert harmful as well as desirable effects.

6. Anemia. It has been suggested that the anemia of chronic nephritis is due to the retention of phenols. Certainly the closely related benzol causes marked depression of hematopoietic function. Becher (1919) observed a parallelism between the rise of the free phenols in blood and the severity of the anemia in patients with renal insufficiency. Tönnis (1933) has recently reported the development of severe anemia in dogs with a large blind pouch in the intestines. The anemia was ascribed to excessive putrefaction with the formation of phenolic derivatives of the aromatic amino acids.

7. Changes in the skin. Purpuric manifestations are frequently observed in uremic subjects and we are not aware of any satisfactory explanation for their occurrence. Conceivably calcium ion deficit may be concerned by delaying blood clotting time and increasing capillary permeability [Osterhout (1922)]. It is of interest that animals dying of guanidine intoxication usually exhibit hemorrhages into the gastro-intestinal mucosa.

Yellowish pallor of the skin is frequently seen in uremic subjects. This is believed by Becher (1925) to be due to retention of urinary chromogens. This author has pointed out that these substances are oxidized in the exposed portions of the skin to the corresponding pigments and believe that this mechanism accounts for the predominance of the yellowish color in the face and hands.

The numerous *other alterations in the skin* which may occur in persons with renal insufficiency are dependent on obscure mechanisms. The causes of pruritus and the several forms of uremic dermatitis are still unknown. Because of the impairment of their excretory processes, uremic patients are very susceptible to intoxication by drugs and some of the eruptions which have been ascribed to uremia can be accounted for by medication with doses which ordinarily do not affect the skin. Alterations in the skin due to dehydration or to the deposition of urea (the "urea frost") are, of course, clearly understood.

VI. THE PRINCIPLES OF THERAPY IN PATIENTS WITH UREMIA

Critical discussions of the treatment of renal insufficiency have recently been published by Becher (1933) and by Fishberg (1935). The following general principles seem to be especially significant.

1. Attempts to improve renal function. Here it is of first importance to differentiate between removable causes of uremia, such as obstruction and infection in the urinary tract, and irremediable causes such as nephrosclerosis. It should be remembered that these conditions are not mutually exclusive; prostatic hypertrophy, ureteral stones, or pelvic tumors may add an especially important, because curable, element of renal failure in a patient supposed to be suffering from uncomplicated chronic nephritis. Even in the latter disorder an acute exacerbation with edema and congestion of the kidney may precipitate the uremic state which under such conditions is not entirely hopeless because intensive therapy may prolong life until some healing of the renal tissue can take place. When, as is usually the case, renal insufficiency is due entirely to a progressive sclerosing process in the kidney significant improvement cannot be expected to occur.

Frequently uremia is initiated by congestive heart failure and therapy directed to the heart may be life-saving. In such cases the manifestations of uremia may be postponed for many months by overcoming the additional impairment of renal function produced by congestion.

Severe dehydration due to polyuria, vomiting or diarrhea may of itself cause impairment of renal function and restoration of the body fluids produces corresponding amelioration of the renal condition.

2. Diminution of the load on the kidneys. A low protein diet is of obvious advantage. The food should be abundant in carbohydrate in order to maintain nutrition and diminish the destruction of body protein. Liver function may be improved by glucose which should be administered parenterally when vomiting interferes with carbohydrate intake. Hoesch (1932) recommends insulin in uremia for its beneficial effect on the liver. Becher (1933) has suggested that the necessary protein be given in the form of gelatin because this compound is relatively free from the aromatic amino acids which are the precursors of the phenolic substances.

The burden on the kidneys is often aggravated by the occurrence of pre-renal azotemia in patients with excessive vomiting. Here restoration of body fluids and the administration of salt, when hypochloremia exists, may be helpful.

3. Increasing elimination by routes other than the kidney. Sweating and catharsis are time honored remedies not without their disadvantages. Becher (1933) has emphasized the value of constant duodenal drainage, a procedure which not only eliminates waste products, but tends to protect the gastro-intestinal mucosa from the untoward effects of ammoniacal fermentation [Hessel and Pekelis (1933)]. Attempts have also been made to utilize the peritoneum as a dialyzing membrane and to get rid of retained products by introducing isotonic glucose solution into the abdominal cavity and later removing it [Jeney (1932)].

4. Symptomatic treatment. The value of lumbar puncture and of venesection in the treatment of headache, vomiting and convulsions are well known. Acidosis may be relieved by the judicial administration of sodium bicarbonate. Twitchings can usually be abolished by injection of calcium salts either intravenously [Fishberg (1935)] or intracisternally [Mason et al. (1936)].

When considered from the standpoint of their therapeutic application the advances made in the understanding of the pathogenesis of uremia during the past two decades are rather disappointing. Although in uremia due to acute nephritis and to surgical disorders of the urinary tract much may be accomplished, the treatment of renal insufficiency associated with the contracted kidney remains in a most unsatisfactory state. It can never be otherwise when one is dealing with the end results of a functional disorder due to scar tissue. Advances here must come rather from an understanding of the mechanisms of arteriolar disease, hypertension, and the renal damage produced by infection.

VII. CONCLUSIONS

Out of the mass of work dealing with the complex subject of renal insufficiency certain generalizations emerge.

"... the century old search for an 'uremia toxin' has been fruitless; we do not yet know any single substance the retention of which, as a result of renal insufficiency, produces uremia.... Uremia is a complex autointoxication, the variegated clinical picture being the summation of the effects of retention of various urinary constituents ..."

This concept of the multiple etiology of uremia, so clearly expressed by Fishberg (1935), is well illustrated by the mechanism of the symptoms referable to the nervous system. Certain substances tend to produce increased neuromuscular irritability; others cause depression; the final state is dependent on the balance between these antagonistic influences.

The retention of certain urinary substances themselves relatively innocuous end-products of metabolism, may lead to the accumulation of their poisonous precursors, or to deficiency in the composition of the *milieu intérieur*. Thus relatively harmless substances may become indirectly toxic.

A known and definite rôle in the pathogenesis of uremia can be ascribed to a few substances. Calcium ion deficiency as the result of the retention of products forming unionized calcium salts is concerned in the initiation of motor irritative phenomena; phenol derivatives are related to the stuporous state; accumulations of organic and inorganic acids, as well as loss of base, play a rôle in the production of respiratory disturbance; depletion of chloride and of water increase the catabolism of protein and at the same time impair further the ability of the body to excrete the resulting metabolites.

There is strong evidence that other substances are also of pathogenetic significance. Guanidine-like compounds occur in excess in the blood and seem to play a rôle in the production both of motor irritative phenomena and of gastro-intestinal disturbances. Urea accumulation may be harmful either by initiating excessive ammoniacal fermentation in the alimentary tract, or by interfering with the processes of detoxification.

At the present time it is possible to account for most of the clinical manifestations of uremia on the basis of alterations in the concentration of known compounds in the *milieu interieur*. However, there is reason to believe that some and possibly many undefined substances are also concerned. In the final analysis the uremic death of the most highly integrated organism is strictly comparable to the dissolution of the most simple organism in an aging bacterial culture—both are destroyed in an environment poisoned by the products of their own metabolism.

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TUBERCULOUS PERICARDITIS

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INTRODUCTION

The occurrence of clinically important tuberculosis of the pericardium is not infrequent. The majority of the reports concerning this lesion have been based on anatomical studies, and the clinical descriptions have, for the most part, been limited to single case reports. During the past 45 years 95 cases of tuberculous pericarditis have been admitted to the Johns Hopkins Hospital. An analysis of this series has been undertaken in order to present more clearly the clinical picture of this form of tuberculosis. No attempt has been made to review completely the contributions on this subject, but only the more important articles have been mentioned.

The term primary tuberculous pericarditis has had several definitions. By some it is regarded as including only those cases in which no other tuberculous lesion can be found at autopsy. This type is more correctly designated as the anatomically primary form, but must never occur. Generally it is used in reference to those cases in which active tuberculous lesions elsewhere in the body cannot be demonstrated at the onset of symptoms, the so-called clinically primary type. The term "primary" is unsatisfactory as the pericarditis is always secondary to some other tuberculous lesion. The cases can be better divided into those in which the pericarditis was the most important factor in the production of the clinical picture, and those in which it occurred during the course of a disseminated tuberculosis and did not produce clinical signs or symptoms.

Rokitansky (16) is credited with being the first to comment on primary tuberculous pericarditis. He states that it often occurs in combination with inflammation of other serous sacs, and that it is associated with and dependent upon an earlier tuberculous lesion. According to Noscov (11) the first reported case of primary tuberculous pericarditis was by Quinquand and Lejard in 1872. An excellent clinical discussion is that presented by Osler (13) in 1893 who reported 17 cases.

Reisman (15) in 1901 defined the clinically primary type as that in which active tuberculous lesions elsewhere in the body could not be demonstrated at the onset of symptoms. Using Reisman's criterion Clarke (3) in 1929 stated that careful search revealed only eleven such cases on record in which the diagnosis could not be questioned, and in which there was an adequate clinical history. He reviewed these eleven cases and reported two more. Roubier and Dubois (17) reviewed 1300 autopsies and found five cases of tuberculous pericarditis. The youngest patient was 67 years of age. They stressed the incidence of this lesion in elderly people, and stated that Lejard (Paris thesis 1884–5) first mentioned this fact. Thompson (22) in 1933 reviewed 21 so-called anatomically primary cases, all of which occurred in old people, and were associated with signs of progressive heart failure. He also presented seven similar cases. In several of these, however, there were either old inactive tuberculous lesions or evidence of recent miliary spread.

Bellet, McMillan, and Gouley (2) in 1934 reported a clinical and pathological study of 17 cases of tuberculous pericarditis. They concluded that it is not a rare condition, and that it occurs most often in children and young adults. It is predominantly a disease of the colored race. In the healed state it presents the histological picture of a non-specific chronic fibrous pericarditis. They emphasized the importance of the finding of tubercle bacilli in the pericardial fluid, the demonstration of a small heart after the production of a pneumopericardium, and the absence of cardiac murmurs in distinguishing this condition from rheumatic pericarditis with effusion. They stated that congestive heart failure is usually absent except in the terminal stage in tuberculous pericarditis.

In order to facilitate a clear analysis of the clinical picture in the 95 cases of the present series, they have been divided into the following groups:

I. Proven cases of clinically important tuberculous pericarditis.
    A. Pericarditis with a large effusion (over 300 cc.)—20 cases.
    B. Pericarditis without effusion—17 cases.

II. Unproven cases of clinically important tuberculous pericarditis.
  A. Pericarditis with signs of a large effusion—31 cases.
  B. Pericarditis without effusion—3 cases.
III. Proven cases of tuberculous pericarditis in which the pericardial lesion was of no clinical importance—24 cases.

After an analysis of each group of cases, a comparison will be made between the proven and unproven clinically primary cases, and cases of rheumatic pericarditis with effusion. From this comparison it will be shown that the clinical course of these unproven cases is very similar to that of the established cases of primary tuberculous pericarditis.

A follow-up study has been made of some of the cases included in Group II. In view of the statement by Sprague, Birch, and White (20) that tuberculosis of the pericardium of the insidious type is the most probable cause of the constricting pericarditis of Pick, additional information should be gained from the present series in regard to this possibility.

PROVEN CLINICALLY IMPORTANT TUBERCULOUS PERICARDITIS WITH EFFUSION

This group, comprising 20 cases, is the most important and at the same time one of the most interesting of the series. The cases occur during almost every decade of life. Twenty-five per cent occurred between the ages of 20 to 30, but seven of the 20 were over 50 years of age. It is predominantly an illness of males as 90 per cent of the patients were of this sex. The prevalence of the disease in the colored race is quite striking, 15 or 75 per cent being negroes. A past history of tuberculous symptoms, and any history of tuberculosis among members of the patient's family were conspicuously absent. Two only gave a history of tuberculosis in the immediate family, and one patient had had an hemoptysis in the past. Likewise a story of cardiac disease or rheumatic manifestations in the past was an infrequent finding. Three patients gave a vague story of joint pains six to eleven years previous to the present illness. The story was not that of a typical rheumatic polyarthritis, and in no instance was there a history of symptoms suggestive of myocardial insufficiency up to the onset of the present illness.

The mode of onset and progression of the symptoms and signs up to the time of admission were characteristically slow. Frequently noted at the onset were malaise, weakness and anorexia. Cough was a prominent early symptom and developed shortly after the onset in three-fourths of the cases. Pain, if complained of, usually appeared fairly soon. Dull, vaguely localized, chest pain was the most common type, and was present in 25 per cent of this group. In two instances the patient came to the hospital complaining of severe agonizing pain in the chest which was aggravated by respiration. Pain at the tip of the shoulder, and a sensation of precordial fulness each appeared once. As most of the patients belonged to the colored race, very little reliance can, however, be placed on such a subjective manifestation as pain.

The most prominent complaint in almost every case when the patient was first seen was shortness of breath. Slight exertional dyspnoea commonly appeared shortly after the onset, gradually progressed until present on the slightest movement. This symptom was noted in 85 per cent of the cases. Edema, recognized as ankle edema, and in some instances as swelling of the abdomen, usually appeared after dyspnoea, but rarely was the first complaint.

Although cough was almost always a prominent symptom, in only five instances was there any sputum present. This was clear and mucoid in character. Hemoptysis occurred in two. Other symptoms commonly found in tuberculosis such as night sweats and weight loss were present in about 20 per cent of the patients. The average duration of the minor symptoms before medical advice was sought was seven weeks. The average duration of the period of dyspnoea was four weeks. Only five patients gave a history of fever accompanying their illness. Other symptoms which were more occasionally noted were: nausea, vomiting, diarrhoea, palpitation, headache, delirium, nocturia, eructation, and a sense of epigastric fulness.

The findings at the time of admission were not always characteristic of pericardial effusion, and many times the correct diagnosis was not suggested when the patients were first seen. Often because of signs of compression at the base of the left lung or a pleural friction rub, bronchopneumonia was thought to be present and the cardiac manifestations were overlooked. In other instances arteriosclerosis was thought to be the cause of the heart disease, or uremia with pericarditis was considered possible.

In the cases with good sized effusions, however, the picture was usually so characteristic that no difficulty was experienced in making the correct diagnosis. In 95 per cent of the cases the cardiac dulness was increased to the right and left with accompanying widening at the base. No cardiac impulse could be seen or felt in 11 of the 20 cases, in eight it was described as faint, and in only one was a forceful beat present. Usually the sounds were weak, distant, tic-tac, or described as foetal in quality. A pericardial friction rub was present in only six (one-third) of the cases before fluid was removed from the pericardial sac. Tachycardia was almost uniformly present. The absence of significant cardiac murmurs was quite striking. In four cases a faint systolic bruit was heard, but in 16 cases there were no murmurs at all present. Abnormalities of rhythm in the presence of a pericardial effusion are of great interest. Auricular fibrillation was found in two cases of this group. The average blood pressure showed no particular deviation from normal, the figures being: systolic 120 mm./Hg., diastolic 85 mm./Hg. with a pulse pressure of 36 mm./Hg. A paradoxical pulse confirmed by respiratory variation of measurable degree with the sphygmomanometer occurred in seven of the 20 cases. A frequently mentioned sign of pericardial effusion, an obtuse cardiohepatic angle, was described in only three cases—in our experience a sign of little importance. Signs of pulmonary compression which sometimes led to a diagnosis of pneumonia were quite variable in character and were present in 60 per cent of the group. Usually dulness with suppressed breath sounds and a few crepitant râles were discovered, but in only seven were the typical findings those described by Ewart. One of the most reliable aids in making the diagnosis was displacement downward of the left lobe of the liver by the effusion, present in 55 per cent of the cases.

Physical signs and symptoms attributable to the increased intrapericardial pressure, and resulting tamponade of the heart were almost always in evidence. The typical clinical picture of congestive heart failure was seen often. The neck veins were engorged in 12; edema was present in 12; ascites was noted six times; liver enlargement occurred in 11; and moist râles appeared at both lung bases in four. Usually the edema was of the dependent type and involved the legs and genitals. In some, however, edema over the upper half of the body and face was evident. Dyspnoea at rest and cyanosis of a

CHART 1

Characteristics of the pericardial fluid

	PROVEN CASES		UNPROVEN CASES	
Number of cases examined	20		11	
Appearance:				
Sero-sanguineous	14		9	
Straw colored	1		1	
Yellow-green turbid	5		1	
Red blood cells:				
Average number	334,500 per cu. mm.		360,000 per cu. mm.	
Maximum number	2,100,000 per cu. mm.		920,000 per cu. mm.	
Lowest number	210 per cu. mm.		650 per cu. mm.	
Amount of fluid:				
Maximum at one time in pericardial sac	3,500 cc.			
Maximum withdrawn at one tap	1,650 cc.		1,250 cc.	
Largest total amount withdrawn in one case	5,885 cc.		1,855 cc.	
Number of cases with total amount above 1,000 cc.	11	includes autopsy		
Number of cases with total amount below 1,000 cc.	9			
White blood cells:				
Average number	7,829 per cu. mm.		3,800 per cu. mm.	
Maximum number	54,000 per cu. mm.		18,000 per cu. mm.	
Lowest number	658 per cu. mm.		380 per cu. mm.	
	Polymorphonuclear	*Mononuclear*	*Polymorphonuclear*	*Mononuclear*
Differential count: Average number	27%	73%	37%	64%
	1 case 0%	100%	2 cases 0%	100%
	1 case 85%	15%	1 case 68%	32%
Specific gravity:				
Average	1.018		1.023	
Highest	1.023		1.033	
Lowest	1.015		1.018	
Albumin:				
Average	41 grams per liter		38 grams per liter	
Maximum	96 grams per liter		60 grams per liter	
Minimum	8 grams per liter		12 grams per liter	
Other laboratory tests				
White blood cells: Average	6,974		5,340	
Hemoglobin: Average	79%		82%	
Urine	No significant abnormalities		No significant abnormalities	

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recognizable degree were less often found. With the exception of the signs resulting from compression of the lung very few pulmonary abnormalities developed. Pleural effusion was present in three cases on the right and in two on the left. A pleural friction rub was heard twice; and in an equal number of cases a pleuro-pericardial friction. Signs of pulmonary involvement were found in only 15 per cent. In no instance was there extensive pulmonary involvement or cavity formation. Weight loss was evident in 60 per cent of the cases.

Thus one can see from the course of development of tuberculous pericarditis with effusion that the disease begins insidiously with the appearance of signs and symptoms attributable to a chronic infectious process. As the illness progresses signs and symptoms due to the accumulation of fluid in the pericardial cavity appear, and are often the most outstanding feature at the time of admission to the hospital. One striking feature is the relative mildness of the complaints of the patient in contrast to the high fever and obvious seriousness of the condition.

The important laboratory findings are recorded in chart 1. A mild anemia and a normal white blood cell count were usually found. The pericardial fluid was typically a sero-sanguineous exudate. Urine examination showed no important abnormalities. In this series of cases the most efficacious point for paracentesis of the pericardium was found to be outside the apex beat, but just inside the left border of cardiac dulness.

Sixteen of these patients died, and autopsies were obtained on 15. Of the five patients not autopsied tubercle bacilli were found in the pericardial fluid in four, and in the remaining one a biopsy of the thickened peritoneum showed tuberculous granulation tissue.

THE COURSE OF THE PROVEN CASES WITH EFFUSION

The course of the disease in these patients is quite characteristic. The average duration from the onset of symptoms until the termination was 3.7 months. The age was a significant factor. In five cases over 50 years it was nine weeks, while in eight cases under 50 years it was 18 weeks. A progressive downhill course was noted in 15 of these cases. One of the group recovered from the illness associated with pericarditis, but four years later developed tuberculous peritonitis with marked ascites, and one died of tuberculous meningitis eight months after discharge. Two cases were followed for six months and one for ten months. At the end of that time marked improvement had ensued and the patients never returned for further observation.

The temperature in these cases was typically high and swinging. There was often a range of 3 to 4 degrees during the day with the maximum rise reaching 103 to 105 degrees. The tachycardia was proportional to the fever in most instances. Toward the end of the illness or during a period of improvement the fever subsided but the increase in pulse rate almost invariably persisted.

The illness during the stay in the hospital was dominated by one of two features, —myocardial failure or the development of other forms of tuberculosis. In sixteen instances characteristic evidences of cardiac insufficiency were described. In many the dyspnoea, moisture at the lung bases, liver enlargement, and edema were slowly progressive until death. In four of the patients pericardial disease and myocardial insufficiency were the only manifestations. A conspicuous cardiac arrhythmia developed in five patients. In three a transient auricular fibrillation occurred, and in two frequent extrasystoles interrupted the normal rhythm. The latter patients were receiving digitalis at the time. Pulmonary infarction was a terminal complication in two instances. In one other patient thrombosis of the left saphenous vein was noted during the illness. The sudden onset of pulmonary edema was the cause of death in two patients.

Other forms of tuberculosis were discovered during life in thirteen cases. Pleural involvement was present in eight, six of which had an effusion. In five the peritoneal cavity was the seat of tuberculosis and ascites was a prominent feature. Meningitis was the cause of death in one. In no instance was extensive lung involvement present, but evidences of pulmonary tuberculosis were found in three cases.

The removal of the pericardial fluid seemed to be a distinctly beneficial procedure. Most of the patients were relieved of their distressing dyspnoea, and the cyanosis became less marked after pericardial paracentesis was done. In each of the four patients who showed marked improvement large amounts of fluid were removed. The influence toward improvement which results when the fluid is aspirated can be seen from the following table:

AVERAGE OF	TOTAL DURATION	HOSPITAL STAY	TOTAL AMOUNT OF FLUID	AMOUNT REMOVED
	weeks	*days*	*cc.*	*cc.*
5 cases with more than 500 cc. fluid at autopsy.	6.4	13	1,832	362
8 cases with less than 500 cc. fluid at autopsy..	20	41	2,206	2,048

Of 12 of the autopsied patients tuberculous lesions outside of the pericardium seemed responsible for death in five. The average age of these patients was 36 years. On the other hand seven died with progressive myocardial failure and had no important tuberculosis except that involving the pericardium. The average age in this group was 47 years. Although these figures are inadequate because of the small group of patients, they seem to indicate that the poor prognosis in the older patients is associated with the inability of the cardiovascular system to cope with its added burden, while in the younger cases the frequency of development of other serious tuberculous lesions is responsible.

PROVEN TUBERCULOUS PERICARDITIS WITHOUT EFFUSION

These 17 cases all had tuberculous pericarditis without a recognizable effusion during the period of examination in the hospital. In no case was fluid obtained by paracentesis or found at autopsy. It is probable that at an earlier stage of the disease fluid was present. An autopsy was obtained on 15, and in the other two tubercle bacilli were found in the sputum. All were male and ten were colored. They occurred in all age groups. A family history of tuberculosis was obtained in four. Six admitted past symptoms suggestive of tuberculosis. Hemoptysis and cough were present twice, night sweats three times, pleurisy and dyspnoea each once. A story of vague joint pains in youth was obtained from one patient, but there was no other history of rheumatic manifestations or of heart disease.

The symptoms complained of by this group were similar to those of the patients with large pericardial effusions. Beginning from a week to several months before admission, the incidence of chest pain, dyspnoea, cough and malaise was very common. Dyspnoea frequently was progressive. Edema occurred somewhat less often. Anorexia, weight loss, night sweats, hemoptysis and a productive cough were infrequent complaints. Likewise, the physical examination on admission presented findings similar to the previous group, and from a study of these cases the differential diagnosis between fluid in the pericardium and a greatly thickened pericardium could not be made. In the cases with effusion a few signs were observed with greater frequency. Engorged neck veins, absent point of maximal impulse, very large hearts, pulsus paradoxus, and Ewart's sign occurred more often, but were present in a sufficient number of the cases of this series to render them of little value in the differential diagnosis. Pericardial friction rubs were heard in 30 per cent of the cases of Group I and in 44 per cent of those of Group II. Consequently, a large effusion does not prevent the appearance of a friction rub. Laboratory data, too, were almost quantitatively the same.

The course of the illness of these patients was fairly typical. From unreliable histories the duration to death of 15 cases averaged five months. Of seven cases under 40 years of age the average duration was six months, while eight over 40 lived four months from the beginning of symptoms. Thus, in general, the younger patients withstood the disease longer than the older ones. Likewise, there was a difference in the clinical pictures presented by the two age groups.

Of eight cases under 45 years of age the clinical impression was miliary tuberculosis in three, pulmonary or peritoneal tuberculosis in five. They ran a swinging fever of 100° to 103° F., tachycardia, normal or slightly elevated white blood cell counts, and mild anemia. Five had signs of pulmonary tuberculosis during life, and six had miliary or disseminated lesions at autopsy. The course was dominated by signs of widespread tuberculosis, undoubtedly the primary cause of death. Of nine patients over 45, five had the signs and symptoms of progressive myocardial insufficiency. These presented the picture of constrictive pericarditis during life. The three with swinging fever may be classified as active tuberculous pericarditis, and the two without fever fall into the group of chronic constrictive pericarditis. All five resemble one of the original cases reported by Pick (14), and some of the cases of Pick's disease reported by White (23). Two of White's patients on whom pericardial resection was performed and "who died primarily of the lesion itself," and one "who died of complications" had tuberculous pericarditis, and in the former two the process was still an active one. In our cases ascites was not a predominant feature. At autopsy there was active pericarditis and chronic passive congestion of the liver.

CASES IN WHICH TUBERCULOSIS OF THE PERICARDIUM WAS RELATIVELY UNIMPORTANT

This group, made up of 23 cases in which the pericardial lesion was not important, is analyzed to learn more about its incidence and distribution, and its association with tuberculosis of other organs. Certain differences from clinically primary pericarditis will be brought out. In none of these cases was the diagnosis of pericardial involvement made during life. The clinical diagnoses all concerned the various other forms of tuberculosis present. Autopsies were performed on every case.

Thirty per cent of the cases were under ten years of age, and 50 per cent were younger than 20. The 50 per cent between 20 and 70 were evenly divided in the various decades. Seventy-four per cent were in males. Colored patients outnumbered whites in the ratio of almost five to one. The most important tuberculous lesions described during life were: pulmonary tuberculosis, nine cases, of which two had cavities; pleural effusions, five, of which tubercle bacilli were found in one effusion; tuberculous peritonitis, three; tuberculous empyema, one; tuberculous pyopneumothorax, two; tuberculous pneumothorax, one; tuberculous meningitis, two.

There were few cardiac signs suggesting pericarditis. The heart was enlarged in four cases, and there was a systolic retraction in one. The point of maximum cardiac impulse was difficult to see or feel in six. The heart sounds were distant in four. Two cases presented pericardial friction rubs. Systolic murmurs were heard five times and extrasystoles occurred once. In one case there was dependent edema. In one case in which a pericardial rub was present, the rub developed during the child's stay in the hospital, and at autopsy recent miliary tuberculosis with miliary tubercles on the pericardium was found. In the other case with a pericardial friction, there was at autopsy a pyopneumothorax with involvement of the pericardium from without. Thus, this group of 24 patients all died of tuberculosis, and over 50 per cent were found to have miliary involvement. At autopsy evidence of tuberculous pericarditis was present in all, but in only a few was there sufficient involvment to give clinical signs of a pericardial lesion. These patients were of the younger age groups, and during life showed extensive pulmonary, pleural, meningeal and peritoneal tuberculosis.

UNPROVEN CLINICALLY PRIMARY TUBERCULOUS PERICARDITIS

This group is comprised of 34 cases, in 11 of which the pericardial fluid was removed by paracentesis. In 20 others there was sufficient clinical and laboratory data to be certain of the presence of a pericardial effusion. In three cases the evidence pointed to an active pericarditis without significant amounts of fluid. They occurred in all age groups. Twenty-five were in males, six in females. Twenty-six were colored and only five white. In only four was a family history of tuberculosis obtainable, and in 27 it was specifically denied. Only seven gave any past history suggestive of tuberculosis; four had had night sweats, two a cough, one pleurisy with effusion, and one tuberculous involvement of the wrist. A past history of rheumatic manifestations was absent.

The symptoms and signs present in these cases were so entirely similar to the proven cases that they may be briefly enumerated. Dyspnoea, chest pain, edema, and malaise were generally the complaints on admission to the hospital. Physical examination usually revealed patients with mild dyspnoea, most of whom did not seem as severely ill as the temperature, pulse rate, and findings on physical examination indicated. An enlarged cardiac outline with distant heart sounds, no murmurs, pericardial friction rub, signs of compression of the lungs and a palpable displaced liver occurred with almost the same frequency as in the proven cases. Distention of the neck veins, a paradoxical pulse, edema, ascites, and a pleural friction rub were also of frequent occurrence. None of these patients had physical signs of extensive pulmonary tuberculosis. In nine cases in which the sputum was examined, tubercle bacilli were found in none. Of fifteen tuberculin tests, eleven were positive in high dilutions and four were negative.

A pericardial paracentesis was performed on eleven patients. In almost every case the fluid had the characteristics of a sero-sanguinous exudate, and bacteriological examination revealed no organisms. (See chart 1.)

These 34 patients spent an average of 53 days in the hospital. Two died, one was not treated, one was unimproved and the remaining were discharged improved. The patients who recovered presented a picture of severe infection with cardiac insufficiency, and pursued a fairly typical course. The fever was swinging in type, from 100° F. to 103° F., and gradually decreased to normal over a period of one to two months. The tachycardia, with a rate of 110 to 130, slowly fell to a rate of 90 to 110, but this rapid rate continued even when the temperature became normal. With the decline of fever, the cardiac outline became smaller until it reached a point slightly above the upper limits of normal. The pericardial friction rub was transient, the heart sounds gradually grew louder but still remained somewhat muffled, and the signs of heart failure and pulmonary compression slowly disappeared. No evidence of valvular disease developed. The blood pressure did not change significantly. A persistently normal or slightly elevated white blood cell count, and a mild but not increasing anemia was the rule. The signs of pleural involvement were of short duration, and in no instance did signs of parenchymal extension or disseminated tuberculosis occur. None developed the signs of an adhesive mediastino-pericarditis while on the ward. On discharge, except for slight enlargement of the heart, distant heart sounds and tachycardia, no other abnormalities referable to the pericarditis or to tuberculosis were present in the majority of cases.

Seventeen of these cases have been followed for a period varying from six months to seven years, over an average of three years. The note is made that one developed portal obstruction and signs of adhesive mediastinitis seven years after apparent full recovery. Of the seventeen patients eleven have been examined by the writers. Nine are entirely well and one has undergone three pregnancies with no difficulty. Another now shows clinical signs of adhesive mediastinitis without any evidence of heart failure or exertional dyspnoea. One patient, a 55-year-old colored male, developed a cold abscess in the fourth interspace just to the left of the sternum seven months after recovery from the pericarditis, and tubercle bacilli were demonstrated in the material obtained from the lesion. Another patient, a 25-year-old colored male, was readmitted to the hospital eight months after recovery from the pericardial lesion with signs of spinal cord compression in the region of the eighth dorsal segment. Laminectomy was performed and an epidural mass was found to be compressing the cord in this region. Microscopical section of the tissue showed typical tuberculous granulation tissue and the guinea-pig inoculated died of tuberculosis. Most of the cases who are well have slight cardiac enlargement. This is probably due to a thickened pericardium. None of these cases have developed chronic constrictive pericarditis with the syndrome of inflow stasis. Pericardial calcification has not been demonstrated.

TUBERCULOUS AND RHEUMATIC PERICARDITIS WITH EFFUSION

The differential diagnosis between tuberculous and rheumatic pericarditis is in the majority of instances not difficult. From a study of several cases of rheumatic pericarditis that have occurred in the clinic, and from numerous others reported in the literature, certain differences are apparent. Rheumatic pericarditis occurs usually in children, and a past history of rheumatic fever or heart disease is usually present. On physical examination signs of rheumatic valvular disease are frequently elicited. Thus, in nine cases reported by Antell (1) the ages varied from three to fourteen. Six had a past history of organic cardiac disease or rheumatism. Two of the other three gave a present history of arthritis and one of chorea. Of eleven cases reported by Sutton (21) all had either a past history of rheumatism or signs on admission of valvular lesions. The rheumatic patients usually have a leucocyte count of 10,000 to 25,000, and an anemia of moderate severity develops during the course of the illness. Because rheumatic pericarditis is commonly associated with pancarditis, part of the increased cardiac outline is produced by cardiac dilatation, and the actual effusion is considerably less than in tuberculous pericarditis where myocardial involvement is rare and almost never extensive. In Sutton's (21) eleven cases, on all of whom paracenteses were performed, the average amount of fluid removed at one tap was 265 cc., and the greatest total amount obtained from one patient was 680 cc. In the majority of cases the fluid is yellow and turbid. Flakes of fibrin are often visible, and the fluid coagulates rapidly. The white count of the fluid ranges from a few hundred to several thousand, and polymorphonuclear leucocytes predominate. Cultures are sterile. In a not infrequent number, however, the fluid is serosanguineous or

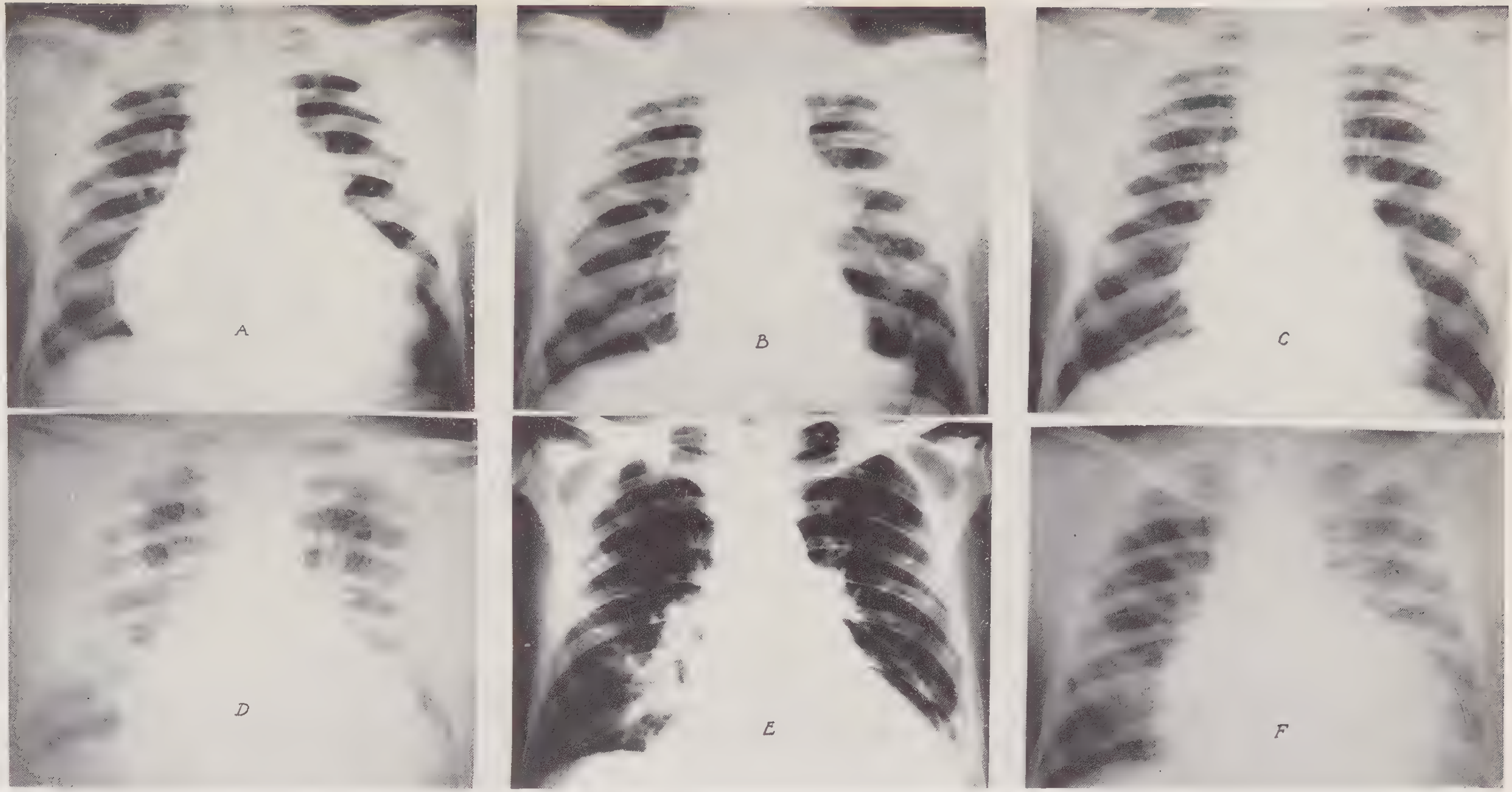

FIG. 1. X-RAYS SHOWING THE VALUE OF PNEUMO PERICARDIUM IN THE DIFFERENTIATION OF RHEUMATIC AND TUBERCULOUS PERICARDITIS WITH EFFUSION

A, tuberculous pericardial effusion. *B*, same case after withdrawal of 1000 cc. of fluid and introduction of 425 cc. of air. The heart is normal in size. *C*, same case 6 months later. *D*, rheumatic pericarditis with effusion, upright position. *E*, same case after withdrawal of 400 cc. of fluid and the introduction of 200 cc. of air. The heart is moderately enlarged. *F*, same case before tapping, prone position, demonstrating change in outline of the cardiac shadow with change of position. All plates are teleoroentgenograms.

distinctly bloody, and thus resembles closely that of tuberculous origin. In the rare case of rheumatic pericarditis without a past history of rheumatic fever, which presents signs of pericardial effusion only, and in which the fluid is hemorrhagic, the differential diagnosis may be very difficult. Even under these circumstances certain factors might aid. After paracentesis murmurs may become audible, and if the fluid is replaced by air, the x-ray may show a large heart shadow surrounded by the air. In tuberculous effusions aside from soft systolic murmurs, no other signs of valvular disease were found, and the cardiac shadow, when outlined by air, was normal. An example in which an acute pericarditis occurring in a colored man twenty-nine years old was misdiagnosed, is afforded by C. R., J. H. H., U-49819. His present illness began suddenly the day before admission with sharp precordial pain. On admission his temperature was 102° F., pulse 120, respiration 50. His heart shadow was enlarged to the right and left, and the heart sounds were almost inaudible. There was a leathery pericardial friction rub, and also a systolic murmur heard only in the axilla. There were signs of cardiac failure. Three productive pericardial taps were performed and 270 cc., 150 cc. and 150 cc. of fluid were obtained. Twice the fluid was hemorrhagic, once turbid yellow. A fourth tap five days before death was dry. He developed transient auricular fibrillation and his course was steadily downhill to death. Because of the patient's race and age, because he showed slight signs of valvular lesion, and because of the hemorrhagic pericardial fluid, the majority who saw him thought he had tuberculous pericarditis. However, certain facts were overlooked. In the 12 years before the present illness, he had had three attacks of joint pains. One year before, he had been seen in the medical dispensary because of pain in the ankles, attributed to pronated feet; then there had been a systolic apical murmur. During his stay in the hospital he had a moderate leucocytosis and anemia. The pericardial fluid that could be removed was of small amount. Consequently, it is not surprising that at autopsy he showed rheumatic heart disease with myocarditis, endocarditis and pericarditis.

THE ELECTROCARDIOGRAM IN TUBERCULOUS PERICARDITIS

In the series of proven and unproven cases with a major pericardial lesion serial electrocardiograms were obtained in thirty patients.

Thirty-three records were made in ten of the proven cases, and eighty-three in twenty cases of the other group. In all but five instances there was an effusion present. Eleven of the patients had digitalis at some time during the course of the illness.

A review of the literature reveals several reports of the electrocardiographic changes in pericarditis. The majority deal with the presentation of a few case reports or some experimental work, but in no instance has the analysis of such a large series as the present one, followed in some instances for over five years, been presented.

In 1923 Oppenheimer and Mann (12) reported a striking decrease in the voltage in seven patients with pericardial effusion. In 1924, Gager (5) described a case of effusion into the pericardial sac in which there was decreased voltage, changes in the RS-T segment with a paradoxical relationship in leads I and III and heart block. These alterations disappeared after the removal of 500 cc. of fluid. Following these reports many single cases were described and emphasis was placed on the deviations in the RS-T segments. These changes were confirmed by the experimental work of Scott, Feil and Katz (19) and later by Hermann and Schwab (18). The latter authors have recently reviewed the literature on the subject and reported seven additional cases. Their contribution to the subject was the notation of progressive late changes in the T waves. The decrease in voltage and the RS-T segment changes usually develop early in the presence of a rapidly accumulating effusion. However, they do not occur in all and are apparently independent of the amount of fluid present. The voltage may even decrease after a pericardial paracentesis.

The usual change is an upward convexity of the RS-T complex followed by a sharply peaked or inverted T wave. Occasionally an iso-electric interval with flattening of the T wave may be the only change. These abnormalities of the period of retreat usually are quite definite by the end of seven to ten days. The T wave changes occur late and are most probably associated with the process of organization and repair in the pericardium. The deviation of the S-T segment has been reported to be always positive and no paradoxical relationship is said to exist between Leads I and III. The T wave usually becomes positive in the chest lead.

Hermann and Schwab (19) report the changes in one case of tuberculous pericarditis. They state that in tuberculous disease of the pericardium with the tendency of the condition to flare-up the changes may continue indefinitely.

The T wave changes are reported to occur alone in fibrinous pericarditis without an accompanying effusion.

In the experiments of Scott, Feil and Katz (9) some animals developed premature contractions, sinus bradycardia, complete heart block, and other arrhythmias which disappeared when the fluid was removed. Similar abnormalities have been described in the human cases.

ANALYSIS OF THE CASES OF THE PRESENT SERIES

The rate. The recorded rate averaged 113 on admission. In one instance it was 160 in the presence of a normal sinus rhythm and in another was only 80 per minute. In seventeen cases the rate was above 110.

Disturbances of rhythm. Abnormalities of rhythm in the presence of a pericardial effusion were not infrequent. In two instances a transient auricular fibrillation developed. In one case this appeared about two weeks after the onset and lasted for only four days. No pericardial tap was done. In the second case it was present when the patient entered the hospital and disappeared almost immediately after the removal of 850 cc. of pericardial fluid. No digitalis was administered to either of these cases. Complete heart block with an auricular rate of 180 and an idioventricular rhythm with 94 ventricular contractions per minute appeared in one case after the patient had been given 1.5 grams of digitalis. The drug was withdrawn and normal sinus rhythm returned. Later digitalis was resumed and the block disappeared. Before death the rhythm again reverted without withdrawal of the drug. In still another case of peculiar ectopic auricular rhythm, a rate of 120 was present to which the ventricles did not respond, impulses were also arising regularly in the normal pacemaker at the rate of 83 per minute, to each of which there was a ventricular response. The P-R interval was 0.14 second. The patient was given 0.8 gram of quinidine sulphate daily and the ectopic beats soon disappeared.

These patients proved quite sensitive to digitalis. In two a first degree heart block and in one a second degree block with a typical Wenckebach phenomenon developed after much less than the required dose, as calculated by the body weight, had been given. As previously mentioned, complete heart block developed on the second day of administration in one patient after 1.5 grams of the powdered drug had been taken. In another, frequent interpolated extrasystoles appeared during digitalis administration.

In 1933, Gouley, Bellet and McMillan (6) reported six examples of tuberculosis of the myocardium. In one case, a boy aged 16, auricular fibrillation was present continually for at least three months before death. In another instance many auricular extrasystoles developed rather suddenly following which the course was progressively downward. They state that it is probable that this disturbance of rhythm may have been the result of the extension of the pericardial process into the right auricular muscle. They believe that the development of ectopic rhythms in patients known to have tuberculous pericarditis is the only possible diagnostic point suggestive of myocardial involvement. In the cases of this series the arrhythmias were either transient or related to the administration of digitalis. In several which came to autopsy there was no evidence of myocardial tuberculosis, and in the one case in which there was invasion of the auricle by the tuberculous process in the pericardium no arrhythmia was present during life.

The changes in the P waves. There were no significant or characteristic changes in the auricular deflections. In the case with complete auriculo-ventricular dissociation the P waves became inverted in all leads each time normal sinus rhythm returned. P III was often small, biphasic or inverted. An increase in amplitude and return to normal form usually occurred after pericardial paracentesis and clinical improvement.

The form of the QRS complexes. Three main types of change may occur in this portion of the electrocardiogram. (*a*) Low voltage: This has always been considered to be a valuable sign and was thought to depend on the presence of a lake of fluid about the heart. Low voltage is said to be present when the QRS amplitude is 5 mm. or less in each lead. Eleven of fifteen patients with an effusion who had records made showed this abnormality. Several observations are of interest which illustrate the fact that this change is not controlled entirely by the amount of fluid present. In one instance the amplitude varied greatly from day to day during a period when much pericardial fluid was present. Over six liters of fluid were removed during the course of the disease in one of the fatal cases but the amplitude of these complexes remained very small. An actual decrease in voltage was discovered after the removal of large quantities of fluid in several instances. It was usual, however, for the height of these deflections to increase as the patient improved and fluid was reabsorbed or removed by pericardial paracentesis. (*b*) Changes in the form and direction of the ventricular deflections during successive cycles: A phasic variation in the amplitude of the QRS complexes associated with respiration was present in many records. This usually disappeared after improvement appeared and was sometimes, but not always, associated with the presence of a paradoxical pulse. Alternation in amplitude was occasionally observed as was change in the form of each second or third complex. These changes were usually present only in the cases with fairly large effusions. In two instances there was complete inversion of the QRS in lead III following a pericardial tap.

The S-T segment changes. The S-T interval changes which occurred in this group are quite at variance with the alterations previously described in the literature. A cove-shaped arching of the S-T segment usually ending in an inverted T wave was a frequent finding. It was present in 15 cases in Lead I, in 17 cases in Lead II, but only three times in Lead III. An S-T segment of opposite contour with a slight downward concavity was present in three cases in Lead III in which the arched S-T segment was present in Lead I. These changes were present as soon as two weeks after the onset of symptoms and if improvement took place usually disappeared within two to four weeks; withdrawal of fluid often had no effect on their form.

An S-T complex arising at some point above or below the isoelectric line was often noted. A deep S wave was usually present when the position of the S-T segment was altered. The changes are briefly summarized in the following table:

	LEAD I	LEAD II	LEAD III
Low S-T take-off	10	8	2
High S-T take-off	1	3	9
Large S wave	5	5	3
Arching of S-T segment	15	17	3

Number of cases, 20.

It is obvious from these figures that the S-T segment deviation was often opposite in Leads I and III. The absence of this change in previous reports has been conspicuous but there is at present no obvious explanation for this fact. Some of the records in this series closely resemble those seen after infarction of the myocardium. The rapidity with which these alterations may change from day to day without the withdrawal of fluid from the pericardium is quite striking. The S-T segment deviations may last for several months if no fluid is removed.

The T wave changes. The alterations in this portion of the electrocardiogram usually appear later than the previously described changes and persist for a longer period of time. From two to four weeks after the onset of symptoms an inverted T wave is usually found in Leads I and II while the deflection remains upright in Lead III or becomes biphasic in character. As healing takes place these deflections gradually resume their original position. The following is a brief chart of the changes as they occur from month to month:

	MONTHS						
	1	2	3	4	6	10	
Lead I:							
Upright	2	0	1	2	1	2	Always up after this
Inverted	9	7	3	5	1	0	
Lead II:							
Upright	1	1	2	2	1	2	Always up after this
Inverted	10	6	2	5	1	0	
Lead III:							
Upright	7	5	3	2	0	2	Occasionally down after this or biphasic
Inverted	4	2	1	4	2	0	

The chest lead. Using Lead V, a total of 28 records were taken on 13 patients. The exploring electrode (right arm electrode) was placed 2 cm. to the left of the left sternal border in the fourth interspace and the indifferent electrode (left leg electrode) on the left leg.

In the early stages the changes paralleled those seen in the conventional leads. The P waves showed no consistent alteration. The QRS complexes were usually biphasic and revealed the same general changes previously described. One difference was that diminution

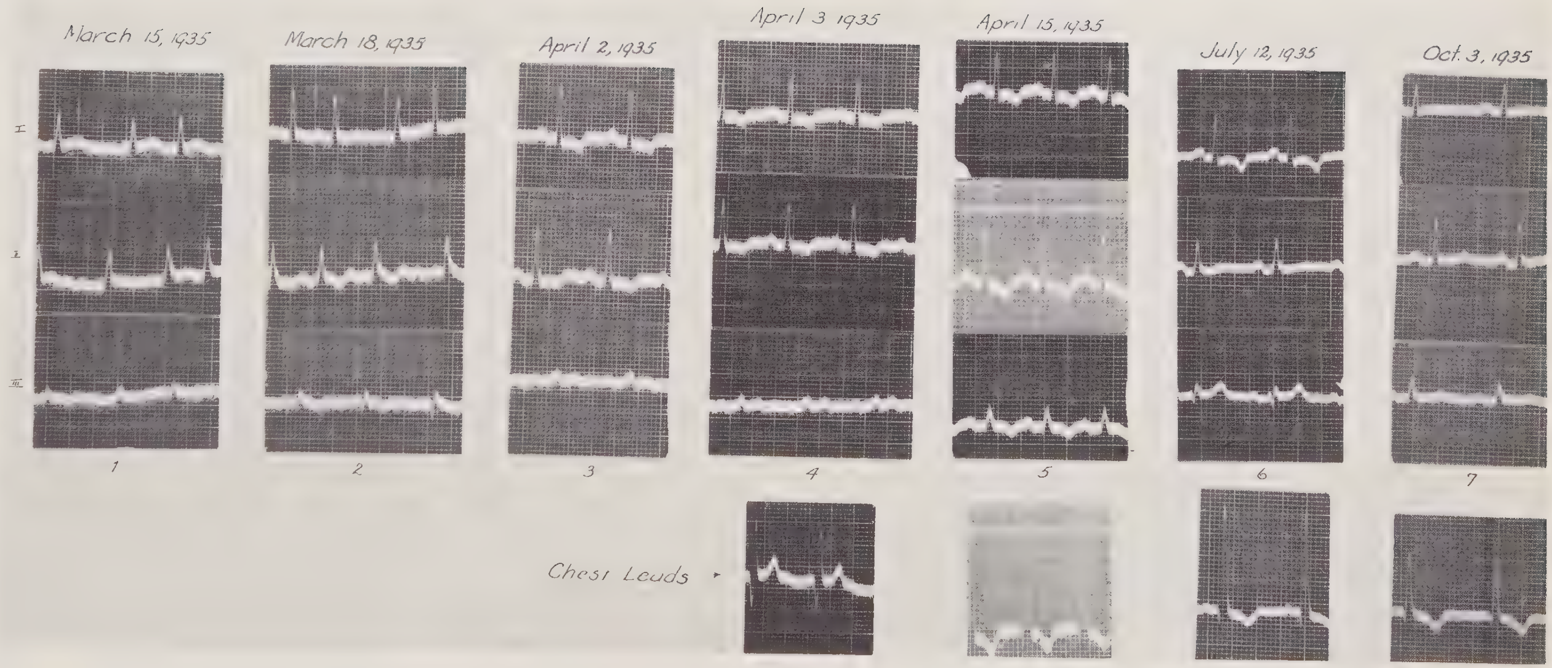
March 15, 1935
March 18, 1935
April 2, 1935
April 3 1935
April 15, 1935
July 12, 1935
Oct. 3, 1935
I
II
III
1
2
3
4
5
6
7
Chest Leads

FIG. 2. SERIAL ELECTROCARDIOGRAMS OF A CASE OF TUBERCULOUS PERICARDITIS

Note the transient auricular fibrillation, and the inversion of the T waves which return to the upright position after seven months. The T wave in the chest lead returns to its normal position somewhat earlier. Figure 3 shows the arching of the S-T interval.

in amplitude was sometimes not present when low voltage was noted in the standard leads. In seven cases seen during the acute stage of the disease the normally inverted T wave was found to be upright. In six of the ten cases observed from seven months to six years after the onset the only abnormality found was an absent Q wave. The remaining four were entirely normal in contour. The T wave usually returns to its normal position several weeks earlier than in conventional leads.

The shift of the electrical axis with change of position. The changes in this regard during the successive periods of the disease are quite interesting. The number of examinations is fairly meager but the results are similar in the different patients. The axis shift was determined nine times in seven patients within the first two months after the onset of symptoms. The average shift with change of position done according to the method of Dieuaide (4) was 16°. Nine determinations in nine patients made from seven months to six years after the onset averaged 17°. The lowest figure was 9° and the highest 37°.

The inversion of the T waves, especially in Leads I and II, may be of prognostic importance and the form of this portion of the electrocardiogram may serve as a guide in the treatment of the patients. Strict restriction of activities and general care should probably be continued as long as inversion of the T waves remains.

RADIOGRAPHIC FINDINGS

The criteria for the X-Ray diagnosis of pericardial effusion and adhesive pericarditis are well known and need only be mentioned here. When the amount of effusion is small or the adhesions thin, considerable difficulty may be encountered, and only by studying successive films for change in cardiac size may the correct interpretation be made. Holmes (7) in 1924 described the roentgenological manifestations of pericarditis, and these apply well to our cases. He stated that: (*a*) in both adhesive pericarditis and pericarditis with effusion it may be impossible to distinguish by fluoroscopy auricular from ventricular contractions, (*b*) there is an increase in the supracardiac shadow and a straightening of the normal curve of the upper portion of the left border, (*c*) there is with effusions a change from a rectangular shape with the patient prone to a water bottle shape with the patient upright, (*d*) there is in the lateral view an obliteration of the posterior cardiac angle, and (*e*) with adhesions the respiratory movements of the heart are limited and the outline irregular. In his cases Rotch's sign or an obtuse cardiohepatic angle was more likely with adhesions than with effusion, but was in both an unreliable sign. In our cases also Rotch's sign could not be demonstrated by X-ray, and this throws doubt on its clinical value. In 1933 Kornblum, Bellet and Ostrum (10) published an X-ray study of seventeen cases of tuberculous pericarditis, and emphasized the importance of the X-ray in arriving at the correct diagnosis. The finding of pulmonary or mediastinal tuberculosis and the demonstration of a normal sized heart after the production of pneumo-pericardium, were used by them as evidence for the tuberculous etiology of the effusion. Pneumo-pericardium also aided in the diagnosis of pericardial adhesions.

In our cases the X-ray was of particular value in corroborating the clinical findings of a cardiac shadow enlarged in all its diameters, in the infrequent case where accurate percussion was very difficult because of a thick chest wall, and in furnishing an exact record of progression or regression of the process. In the few instances in which pneumo-pericardium was produced, it seemed a valuable diagnostic procedure.

TREATMENT

Treatment consists of general measures for the tuberculosis, and relief of the intrapericardiac pressure when it causes cardiac insufficiency. Absolute bed rest for a prolonged period, nutritious diet, sunlight and fresh air aid in combating the general infection. Although in most cases large amounts of pericardial fluid were withdrawn with apparent impunity, in one case 2500 cc. removed in two taps within twenty-four hours may have hastened death. This patient was a 15-year-old negro with huge effusion and signs of marked tamponade. The first paracentesis was followed by moderate symptomatic improvement, but after the second, pulse rate and venous distension increased, and exitus occurred in a few hours. At autopsy the heart was markedly dilated, and the muscle very thin. It would seem safer to withdraw slowly 500 to 800 cc. every twelve to twenty-four hours until signs of heart failure have disappeared. Introduction of air into the pericardium, not more than half as much as the fluid withdrawn, and usually from 300 to 400 cc. may be carried out as a diagnostic procedure after most of the fluid has been removed. From a consideration of the greatly thickened membranes that form, a small amount of air which is rapidly absorbed, can hardly be expected to prevent the formation of adhesions. Inasmuch as these patients seem abnormally sensitive to digitalis and develop cardiac arrhythmias with small doses, and since the heart failure is usually due to cardiac tamponade, the drug, generally, is not indicated. In those patients who continue in failure after the pericardial fluid has been removed, particularly the older ones with arteriosclerosis, it might be useful. Since the few cases in which electrocardiograms were taken for a sufficiently long period finally showed return to normal of inverted T waves, the persistence of this abnormality may possibly serve as a guide for the period of enforced bed rest. After the acute phase has subsided, sanatorium care for 6 to 8 months is certainly wise.

THE PATHOLOGY OF THE PERICARDIAL LESIONS

The anatomical lesions which are characteristic of tuberculous pericarditis have been described previously many times.

Twelve of the present cases which came to autopsy still had a considerable amount of fluid within the pericardial sac. The fluid was usually blood-tinged and varied in quantity from 150 to 3,500 cc. The pericardial cavity was always enlarged and dilated, sometimes extending from the level of the clavicles to the diaphragm. The parietal surface was thickened, leathery and many times nodular tubercles were visible from without. It measured 6 to 8 mm. in thickness. Thick, fibrous, organizing adhesions were occasionally noted which attached the pericardium to the lungs and diaphragm. Upon opening the pericardium the visceral leaf was found to be covered superficially by a mass of thick, shaggy, flaky adherent reddish fibrin, and the strands of fibrin often had a corrugated appearance. Where the two layers were not separated by fluid they were bound together by friable but sometimes fairly thick adhesions.

Below the superficial layer of corrugated fibrin there was a zone of granulation tissue which usually contained many grayish flecks and beneath which the thickened fibrous epicardium was found. The heart with its enclosing fibrinous exudate often weighed as much as 1300 grams, and the wall of the left ventricle plus the shaggy covering sometimes measured 3 cm. in thickness. On section many circumscribed minute yellow opaque points could be seen scattered throughout the tissue. A mass of tuberculous lymph nodes was discovered adjacent to the pericardium in eleven cases and in one instance the actual point of communication with the pericardial cavity could be established. The location of these nodes varied considerably. Most

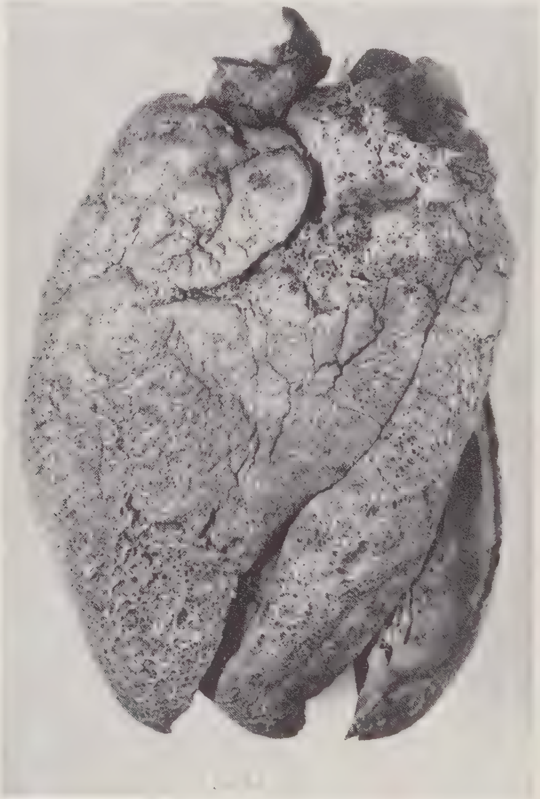

FIG. 3. TUBERCULOUS PERICARDITIS

This photograph shows the corrugated fibrinous deposit upon the epicardium which is thickened.

frequently the peribronchial, peritracheal, and mediastinal nodes were involved, and less commonly the periaortic and anterior mediastinal ones.

Of the cases in which a primary tuberculous pericarditis without effusion was present 16 came to autopsy. The gross pathology in these differed very little from what has just been described. Organization had usually proceeded to a more advanced stage with greater pericardial thickening characterized by a more cartilaginous or rubbery consistency. A fibrinous layer was present, and in many instances there was a fairly definite boundary and the pericardium was easily

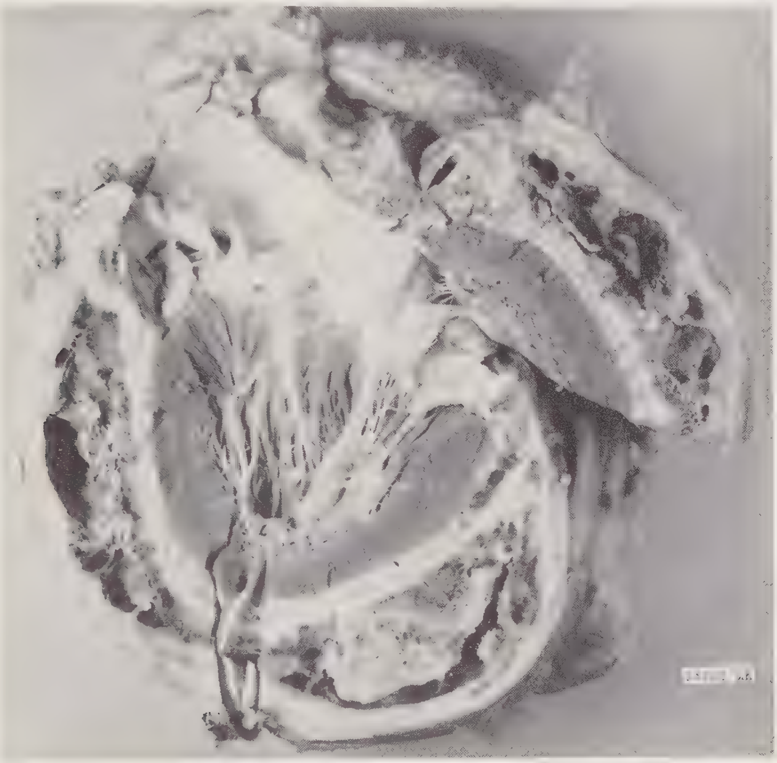

FIG. 4. TUBERCULOUS PERICARDITIS

This illustrated the tremendous thickening of the two layers of the pericardium, the extensive amount of organizing exudate and the pocketing which occurs during healing.

pulled off. However, more areas where the two layers of the pericardial sac were firmly adherent were found. Adhesions to the sternum, lungs and diaphragm were frequently observed. On only three cases were no tuberculous lymph nodes in the thorax discovered.

Twenty-three cases were autopsied in which the pericardial lesion was of no clinical importance. In these the pericardial sac was characteristically obliterated by a web of fibrous tissue. The parietal layer could be torn away exposing a white ragged epicardium. Here numerous hard yellowish nodules were seen, many of which were conglomerate and on section were found to have a necrotic central zone with a grey translucent periphery.

CHART 2

The cardiovascular abnormalities other than pericarditis

LESION	PERICARDITIS WITH EFFUSION (12 CASES)	PERICARDITIS WITHOUT EFFUSION (16 CASES)
Arteriosclerosis	4	2
Coronary arteriosclerosis	1	1
Cardiac hypertrophy	4	5
Cardiac dilatation	3	6
Dilated right ventricle and auricle only	2	3
Auricular thrombi	2	2
Calcification of aorta and mitral valves	1	
Syphilitic aortitis	1	
Chronic passive congestion of liver	5	9
Cirrhosis of liver	2	0

Microscopically subacute to chronic granulation tissue was found. Occasionally this tissue was seen to infiltrate superficially the myocardium, but usually the heart muscle was quite normal.

In this series there is one case of anatomically primary tuberculous pericarditis. The pericardial sac was enlarged, distended and contained 425 cc. of sallow sanguineous fluid. The mediastinal glands were deeply pigmented but otherwise normal. The lungs showed no abnormalities and no other tuberculous lesions were found at autopsy.

The other cardiac abnormalities which occurred and the autopsy indications of cardiac insufficiency are listed in chart 2. Only two cases had cirrhosis of the liver. In one of these there was a slight chronic perisplenitis and perihepatitis. In the other a nodular cirrhosis was found. Neither patient had ascites, and no relation could be established between the liver disease and the pericarditis.

Involvement of the pericardium by an infectious process can occur as a result of trauma, or of direct extension from an adjacent inflammatory focus, or by way of the lymphatics or the blood stream. In the cases in which the pericarditis was clinically important, the high frequency of tuberculosis of the mediastinal lymph nodes and the rarity of other tuberculous lesions suggests strongly that extension from nodes to pericardium occurred in most instances. In the cases of these groups which showed at autopsy disseminated and miliary tuberculosis, these lesions were fresh and seemed to be of terminal origin. In the cases in which the pericardial involvement was not clinically important, tuberculous mediastinal nodes and miliary tuberculosis were frequently present together, and it is difficult to explain precisely the manner of development of the pericarditis. Even in this group there were three instances in which direct extension from the nodes to the pericardium was demonstrated. There were a few other interesting autopsy findings. Amyloid disease was present twice. In one case there was growth of tuberculous tissue into an auricle. The heart was enlarged only three times.

TUBERCULOSIS OF THE MYOCARDIUM

Tuberculosis of the myocardium is rare. The literature upon this subject has recently been reviewed by Horn and Saphir (8). They report three cases of miliary tuberculosis of the myocardium all occurring in children, one of whom also showed a conglomerate tubercle. They conclude that three main types can be differentiated: the nodular, the miliary, and the diffuse infiltrative types. The latter type, they state, should be diagnosed only when the changes are quite characteristic of tuberculosis or if the tubercle bacillus can be demonstrated to be present. The nodular variety, in which the lesions vary from pea-to-egg-size, is the commonest one and is frequently accompanied by some pericardial involvement.

In the present series of cases involvement of the myocardium was very infrequent. In one instance a conglomerate tubercle was found involving the left auricle. It was not large enough to cause any obstruction to the normal flow of blood. In most instances a definite boundary was present between the epicardium and the underlying muscle, but in two instances greyish-yellow tuberculous material was found to dip down into the myocardium. In another case a large hyalinized tubercle was discovered extending from the epi- to the myocardium. Scattered tubercles in the myocardium occurred in one of the patients who died of miliary tuberculosis. A large area of necrosis in the heart bordered by a zone of round cell infiltration was described once but no tubercle bacilli could be stained in the lesion.

The only other heart muscle change was an occasional instance of diffuse scarring associated with arteriosclerosis of the coronary arteries.

SUMMARY

During the past 45 years, 95 cases of tuberculosis of the pericardium have been admitted to the Johns Hopkins Hospital. Of these, there were 71 which were clinically important, of which 37 were proven and 34 unproven. The unproven cases resembled in every respect the proven ones. However, certain differences do exist between the proven and unproven cases. Of 20 proven cases with effusion 16 or 80 per cent died, and 15 of the 17 proven cases without an effusion succumbed, making a total mortality of 83 per cent. This is in striking contrast to the death rate of only 5.9 per cent for the 34 unproven cases. Pericardial fluid was examined during life in 13 cases of the proven group. Tubercle bacilli were found in smears of the sediment of two cases; were cultured in one instance; and were proven to be present by guinea pig inoculation in five. In seven of the 13 cases the diagnosis was proven by smear or guinea pig inoculation of the pericardial fluid. In nine cases of the unproven group tubercle bacilli could not be demonstrated by smear or guinea pig inoculation of the pericardial fluid. We are fully aware of the fact that these rather striking differences may throw some doubt on the tuberculous etiology of the unproven cases. However, the consideration of other important facts makes us believe that there is little doubt as to the correctness of the assumption. In each case the possibility of other known causes of pericarditis has been carefully eliminated. In no case was there a history of rheumatic fever, none of the patients showed evidence at any time of valvular lesions or other rheumatic manifestations, and in the cases in which pneumopericardium was produced the heart was always found to be normal in size. Cultures of the pericardial fluid were in every instance sterile. It is a well known characteristic of the other forms of serous membrane tuberculosis that tubercle bacilli are difficult to recover. Yet, when other causes of pleurisy or peritonitis can be reasonably excluded in these instances, no one hesitates to make a diagnosis of tuberculosis. Of great importance is the fact that 21 of the 34 unproven cases had other tuberculous lesions. There were nine with pleurisy with effusion, and in a similar number mediastinal tuberculosis was diagnosed by x-ray. Roentgenograms revealed lesions of pulmonary tuberculosis in three. Tuberculous arthritis, extradural tuberculoma, cervical adenitis, and a cold abscess were each present once. Tubercle bacilli were demonstrated in these lesions. It is conceivable that in these unproven cases fewer tubercle bacilli were present in those cases which recovered.

The clinically important cases occurred during almost every decade. The illness was predominantly one of males: 85 per cent of the patients were of that sex. The incidence of the disease in the colored race is also striking; 80 per cent of this series were negroes. A past or family history of tuberculosis was infrequent. A past history of rheumatic fever or cardiac symptoms was not obtained. Of these 71 patients, 31 or 44 per cent died while in the hospital, and 35 or 49 per cent were discharged improved. Two were not treated and three were unimproved.

The patients who improved spent an average of 50 days in the hospital. In the majority of the cases, on discharge, outside of a slightly enlarged heart, distant heart sounds, and tachycardia no other abnormalities referable to the pericarditis or to tuberculosis were present.

The patients who died ran a progressively downhill course. The average duration of the disease was a little longer in the younger than in the older ones. The younger patients developed during life and showed at death signs of widespread tuberculosis. The older patients, in general, died from myocardial failure without signs of progressive tuberculosis in other organs. Most of them had low grade fever. At autopsy many showed little besides the greatly thickened tuberculous pericardium and tuberculous mediastinal nodes.

The development of cardiac arrhythmias was an interesting feature.

Two patients developed auricular fibrillation; one, complete heart block; one, a peculiar ectopic auricular rhythm; one, second degree heart block; and two, first degree heart block. These abnormalities of rhythm occurred when the patients were not taking digitalis or had had subdigitalizing doses. The most frequent electrocardiographic changes observed were: low voltage, arching of the S-T segment with deviation from the iso-electric line, and later persistent inversion of the T waves in leads I and II.

Pericardial paracentesis seemed to have a beneficial effect. The cases in which large amounts of pericardial fluid were withdrawn lived roughly three times as long as the patients not tapped. The demonstration of a small heart by the production of pneumopericardium may aid in distinguishing these cases from rheumatic effusions.

From autopsy studies the pericardial involvement appeared to occur most commonly from adjacent caseous tuberculous lymph nodes.

While the pericarditis was still active, some of these cases presented the picture of chronic cardiac tamponade, and resembled reported cases of Pick's disease. We have never seen a patient who recovered from the active process develop chronic constrictive pericarditis with the syndrome of "inflow stasis."

Seventeen cases have been followed for from six months to seven years, and nine are known to be well. One was said to have developed signs of portal obstruction and adhesive mediastinitis seven years after recovery from the acute illness. Pericardial calcification has not been demonstrated in any instance. One case developed tuberculous meningitis; one, tuberculous peritonitis; one, a cold abscess anterior to the pericardium, and one, a tuberculoma of the spinal cord posterior to the pericardium. No other tuberculous lesions have been found in these patients after recovery from the acute pericarditis.

We wish to extend our sincere appreciation to Dr. E. P. Carter for his many valuable suggestions during the preparation of this paper.

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PROVEN TUBERCULOUS PERICARDITIS WITH EFFUSION

Case 1. A. W., U. 56132

Patient's history: Admitted 8/31/31; discharged 10/9/31. Age 13, female, colored.

Other tuberculosis discovered during life: Pulmonary tuberculosis, left lung (X-ray), tubercle bacilli in sputum. Tuberculous peritonitis.

Myocardial failure: Mild. Cleared rapidly.

Amount of pericardial fluid withdrawn: 600 cc.

Tubercle bacilli in pericardial fluid: Stain, negative. Guinea pig, negative.

Duration of disease: 4 years.

Outcome: 3 years after onset; lung clear by X-ray, cardiac shadow a little enlarged, evidence of old mediastinal tuberculosis. 4 years after onset: chronic tuberculous peritonitis. Proven by biopsy.

Comment: Complete recovery from pericarditis with no cardiac symptoms during subsequent 4 years.

Case 2. W. W., U. 62838

Patient's history: Admitted 6/4/35; discharged 6/6/35. Age 15, male, colored.

Other tuberculosis discovered during life: Tuberculous peritonitis.

Myocardial failure: None.

Amount of pericardial fluid withdrawn: 1,900 cc.

Amount of pericardial fluid found at autopsy: 280 cc.

Tubercle bacilli in pericardial fluid: Stain, negative. Guinea pig, positive.

Duration of disease: 1 month.

Outcome: Death.

Other tuberculous lesion at autopsy: Caseous peribronchial lymph nodes. Chronic tuberculosis, left upper lobe. Tuberculous peritonitis. Old tubercles in liver and spleen.

Comment: This patient died in shock a few hours after second pericardial paracentesis.

Case 3. R. B., 19414. Medical bound volume

Patient's history: Admitted 12/12/05; discharged 6/16/06. Age 17, male, colored.

Other tuberculosis discovered during life: Tuberculous pleurisy with effusion. Tuberculous peritonitis. (Fluid negative for tubercle bacilli.) Epididymitis.

Myocardial failure: Mild.

Amount of pericardial fluid withdrawn: 2,430 cc.

Tubercle bacilli in pericardial fluid: Stain, positive. Guinea pig, positive.

Duration of disease: 7 months.

Outcome: Improved. On discharge heart enlarged. No edema.

Case 4. W. H., 12721. Medical bound volume

Patient's history: Admitted 3/31/01; discharged 9/20/01. Age 20, male, colored.

Other tuberculosis discovered during life: Pleurisy with effusion.

Myocardial failure: None.

Amount of pericardial fluid withdrawn: 300 cc.

Tubercle bacilli in pericardial fluid: Stain, positive. Guinea pig, not done.

Duration of disease: 5½ months.

Outcome: Improved. Heart enlarged, tachycardia at time of discharge.

Case 5. M. F., U. 54608

Patient's history: Admitted 12/31/34; discharged 2/5/35. Age 21, male, colored.

Other tuberculosis discovered during life: Meningitis.

Myocardial failure: Mild.

Amount of pericardial fluid withdrawn: 5,885 cc.

Amount of pericardial fluid found at autopsy: 150 cc.

Tubercle bacilli in pericardial fluid: Stain, negative. Guinea pig, positive.

Duration of disease: 5 months.

Outcome: Died of tuberculous meningitis.

Other tuberculous lesion at autopsy: Pulmonary with peripheral lesion. Caseous hilar lymph nodes. Disseminated tubercles in lungs, liver, spleen and bone marrow. Meningitis.

Case 6. W. M., 16910. Medical bound volume

Patient's history: Admitted 3/31/04; discharged 5/2/04. Age 23, male, colored.

Other tuberculosis discovered during life: Pleurisy with effusion.

Myocardial failure: Mild at onset. Progressively more severe until death.

Amount of pericardial fluid withdrawn: 15 cc.

Amount of pericardial fluid found at autopsy: 1,000 cc.

Tubercle bacilli in pericardial fluid: Stain, negative. Guinea pig, negative.

Duration of disease: 2½ months.

Outcome: Died with steadily increasing cardiac insufficiency.

Other tuberculous lesion at autopsy: Bronchial lymph nodes. Pleurisy. Disseminated tubercles in lung, liver, spleen and kidney.

Comment: Died after a course characterized by progressive myocardial insufficiency.

Case 7. W. B., 9467. Medical bound volume

Patient's history: Admitted 1/18/99; discharged 1/19/99. Age 29, male, colored.

Other tuberculosis discovered during life: Sputum positive. No other evidence of pulmonary tuberculosis.

Myocardial failure: None.

Amount of pericardial fluid withdrawn: 1,050 cc.

Amount of pericardial fluid found at autopsy: 2,000 cc.

Tubercle bacilli in pericardial fluid: Stain, not done. Guinea pig, not done.

Duration of disease: 5 weeks.

Outcome: Death five minutes after pericardial paracentesis.

Other tuberculous lesion at autopsy: Caseous peribronchial, peritracheal and pericardial lymph nodes. Rupture of caseous node into trachea. Phlebitis, left innominate vein.

Case 8. E. V., U. 61379

Patient's history: Admitted 3/25/35; discharged 8/2/35. Age 29, male, colored.

Other tuberculosis discovered during life: Pulmonary tuberculosis, pleurisy with effusion; peritonitis, miliary tuberculosis. Tubercle bacilli found in pleural fluid.

Myocardial failure: A pronounced feature with massive edema, great dyspnoea, marked distention of neck veins.

Amount of pericardial fluid withdrawn: 1,050 cc.

Amount of pericardial fluid found at autopsy: 100 cc.

Tubercle bacilli in pericardial fluid: Stain, negative. Guinea pig, negative.

Duration of disease: 17 weeks.

Outcome: Death.

Other tuberculous lesion at autopsy: Active, right upper lobe. Peritonitis. Pleurisy.

Caseous mediastinal and abdominal lymphnodes. Disseminated tubercles, lung, liver and spleen.

Comment: Despite the presence of many other tuberculous lesions, the predominant feature during life was myocardial failure.

Case 9. W. B., U. 27727

Patient's history: Admitted 10/30/29; discharged 11/22/29. Age 32, male, colored.

Other tuberculosis discovered during life: Pleurisy. Pulmonary tuberculosis. Peritonitis.

Myocardial failure: Progressive until death.

Amount of pericardial fluid withdrawn: 530 cc.

Tubercle bacilli in pericardial fluid: Stain, negative. Guinea pig, positive.

Duration of disease: 6 months.

Outcome: Death. No autopsy.

Case 10. J. W., U. 50072

Patient's history: Admitted 6/30/33; discharged 8/28/33. Age 32, male, colored.

Other tuberculosis discovered during life: Pleurisy. Peritonitis.

Myocardial failure: Moderate, not progressive.

Amount of pericardial fluid withdrawn: 2,950 cc.

Tubercle bacilli in pericardial fluid: Stain, negative. Guinea pig, negative.

Duration of disease: 2½ months.

Outcome: Died in acute pulmonary edema following a thoracentesis.

Other tuberculous lesion at autopsy: Old caseous nodule, left apex. Caseous mediastinal and aortic nodes. Pleurisy. Peritonitis. Disseminated tubercles, lungs, liver.

Case 11. E. B., 2213. Medical bound volume

Patient's history: Admitted 7/18/92; discharged 9/27/92. Age 39, female, colored.

Other tuberculosis discovered during life: Pulmonary. Sputum negative.

Myocardial failure: None on admission. Developed later and increased in severity until death.

Amount of pericardial fluid found at autopsy: 300 cc.

Tubercle bacilli in pericardial fluid: Stain, not done. Guinea pig, not done.

Duration of disease: 5 months.

Outcome: Death.

Other tuberculous lesion at autopsy: Cases bronchial and tracheal lymph nodes. Pulmonary. Peritonitis. Enteritis.

Case 12. J. P., U. 26535

Patient's history: Admitted 8/26/29; discharged 12/18/29. Age 41, male, colored.

Other tuberculosis discovered during life: None.

Myocardial failure: Moderate on admission. Gradually cleared.

Amount of pericardial fluid withdrawn: 2,020 cc.

Tubercle bacilli in pericardial fluid: Stain, negative. Guinea pig, positive.

Duration of disease: 16 months.

Outcome: Died suddenly of meningitis 10 months after recovery from pericarditis.

Case 13. E. W., 38946. Medical bound volume

Patient's history: Admitted 12/25/17; discharged 1/13/18. Age 49, male, white.

Other tuberculosis discovered during life: Pleurisy (tubercle bacilli in fluid).

Myocardial failure: Not known.

Amount of pericardial fluid withdrawn: 1,785 cc.

Amount of pericardial fluid found at autopsy: 3,500 cc.

Tubercle bacilli in pericardial fluid: Stain, cultured the bacilli. Guinea pig, not done.

Duration of disease: 2 months.

Outcome: Died with increasing weakness.

Other tuberculous lesion at autopsy: Mediastinal lymph nodes. Pleurisy.

Comment: Probably died of cardiac tamponade and heart failure.

Case 14. H. R., U. 15941

Patient's history: Admitted 12/26/27; discharged 12/29/27. Age 54, male, colored.

Other tuberculosis discovered during life: Pleurisy.

Myocardial failure: Moderate.

Amount of pericardial fluid found at autopsy: 350 cc.

Tubercle bacilli in pericardial fluid: Stain, not done. Guinea pig, not done.

Duration of disease: 3 months.

Outcome: Died three days after admission.

Other tuberculous lesion at autopsy: Disseminated tuberculosis. Old caseous peribronchial and mediastinal lymph nodes. Disseminated patches of caseous pneumonia. Bilateral purulent pleuritis.

Case 15. R. C. W.

Patient's history: Admitted 9/1/03; discharged 9/1/03. Age 59, male, white.

Other tuberculosis discovered during life: None.

Myocardial failure: Moderate.

Amount of pericardial fluid withdrawn: 50 cc.

Amount of pericardial fluid found at autopsy: 1,500 cc.

Tubercle bacilli in pericardial fluid: Stain, not done. Guinea pig, not done.

Duration of disease: Unknown.

Outcome: Died day of admission.

Other tuberculous lesion at autopsy: Caseous bronchial and tracheal lymph nodes.

Case 16. O. D., 1903. Medical bound volume

Patient's history: Admitted 10/5/98; discharged 10/9/98. Age 57, male, colored.

Other tuberculosis discovered during life: None.

Myocardial failure: Mild on admission. Increasing dyspnoea and orthopnoea until death.

Amount of pericardial fluid found at autopsy: 1,100 cc.

Tubercle bacilli in pericardial fluid: Stain, not done. Guinea pig, not done.

Duration of disease: 3 weeks.

Outcome: Death.

Other tuberculous lesion at autopsy: Caseous bronchial and peribronchial nodes. Old latent pulmonary.

Case 17. C. G., U. 30433

Patient's history: Admitted 4/5/30; discharged 8/1/30. Age 60, male, white.

Other tuberculosis discovered during life: None.

Myocardial failure: The increasing degree of cardiac insufficiency characterized his illness.

Amount of pericardial fluid withdrawn: 1,190 cc.

Amount of pericardial fluid found at autopsy: 200 cc.

Tubercle bacilli in pericardial fluid: Stain, negative. Guinea pig, negative.

Duration of disease: 4 months.

Outcome: Died in pulmonary edema.

Other tuberculous lesion at autopsy: Old apical, left lung. Mediastinal lymphadenitis. Fresh disseminated tubercles in lungs, liver, spleen and kidneys.

Comment: The disseminated tuberculosis was not very extensive at autopsy and probably played only a small part in causing death.

Case 18. H. P., U. 47097

Patient's history: Admitted 12/30/32; discharged 1/11/33. Age 64, male, white.

Other tuberculosis discovered during life: None.

Myocardial failure: Advanced failure which progressed until death.

Amount of pericardial fluid found at autopsy: 750 cc.

Tubercle bacilli in pericardial fluid: Stain, not done. Guinea pig, not done.

Duration of disease: 2 weeks.

Outcome: Death.

Other tuberculous lesion at autopsy: Caseous node rupturing into pericardium.

Case 19. A. S., U. 5298

Patient's history: Admitted 6/3/26; discharged 6/29/26. Age 64, male, white.

Other tuberculosis discovered during life: None.

Myocardial failure: Moderate.

Amount of pericardial fluid found at autopsy: 425 cc.

Tubercle bacilli in pericardial fluid: Stain, not done. Guinea pig, not done.

Duration of disease: Unknown.

Outcome: Death.

Other tuberculous lesion at autopsy: None outside of pericardium.

Case 20. J. G., 12065. Medical bound volume

Patient's history: Admitted 10/23/00; discharged 11/20/00. Age 67, male, colored.

Other tuberculosis discovered during life: None.

Myocardial failure: Advanced.

Amount of pericardial fluid found at autopsy: 500 cc.

Tubercle bacilli in pericardial fluid: Stain, not done. Guinea pig, not done.

Duration of disease: 3 months.

Outcome: Died of heart failure. No fever.

Other tuberculous lesion at autopsy: Chronic pulmonary. Caseous pneumonia, right upper lobe.

Proven Cases without Effusion

Case 1. H. Z., 14370. Medical bound volume

Patient's history: Admitted 3/14/02; discharged 7/1/02. Age 17, male, white.

Other tuberculosis during life: Peritonitis. Pleurisy with effusion. Pulmonary (sputum positive for tubercle bacilli).

Myocardial failure: Mild degree.

Duration: 5 months.

Outcome: Unimproved.

Other tuberculosis at autopsy: No autopsy.

Comment: It is difficult to say whether this patient had an effusion at the time of admission. Pericardial friction rub present.

Case 2. A. W., 9163. Medical bound volume

Patient's history: Admitted 11/17/99; discharged 12/21/99. Age 20, male, colored.

Other tuberculosis during life: Pulmonary tuberculosis (positive sputum). Tuberculous laryngitis.

Myocardial failure: None.

Duration: 1 month.

Outcome: Died.

Other tuberculosis at autopsy: Acute fibrinous pleurisy. Chronic pulmonary tuberculosis. Mesenteric adenitis. Tuberculosis of intestines, larynx, kidneys.

Comment: Large heart with pericardial friction rub.

Case 3. H. G., 42281. Medical bound volume

Patient's history: Admitted 6/2/19; discharged 8/16/19. Age 22, male, colored.

Other tuberculosis during life: Miliary tuberculosis.

Myocardial failure: Mild degree on admission which became very severe.

Duration: 3½ months.

Outcome: Died.

Other tuberculosis at autopsy: Tracheo-bronchial lymphadenitis. Generalized miliary tuberculosis.

Comment: Large heart, but no fluid could be obtained. Heart dilated at autopsy.

Case 4. J. W., 19191. Medical bound volume

Patient's history: Admitted 12/30/05; discharged 4/11/06. Age 24, male, colored.

Other tuberculosis during life: Peritonitis. Pulmonary (tubercle bacilli in sputum).

Myocardial failure: None.

Duration: 6 months.

Outcome: Unimproved.

Other tuberculosis at autopsy: No autopsy.

Comment: Large heart with muffled sounds and loud friction rub (pericardial).

Case 5. I. B., 36875. Medical bound volume

Patient's history: Admitted 5/16/13; discharged 5/28/13. Age 26, male, white.

Other tuberculosis during life: Miliary tuberculosis. Pleurisy with effusion.

Myocardial failure: Moderate degree.

Duration: 3 months.

Outcome: Died.

Other tuberculosis at autopsy: Mediastinal tuberculosis. Miliary of lungs, pleura, spleen and liver.

Comment: Calmette 1 per cent positive.

Case 6. W. B., 33027. Medical bound volume

Patient's history: Admitted 9/18/14; discharged 11/17/14. Age 35, male, colored.

Other tuberculosis during life: Pulmonary tuberculosis with apical cavities. Miliary tuberculosis.

Myocardial failure: Moderate degree.

Duration: 6 months.

Outcome: Died.

Other tuberculosis at autopsy: Caseating tuberculosis of lungs, bronchial, mesenteric and retroperitoneal glands. Miliary tuberculosis of liver, kidneys and peritoneum.

Case 7. J. P., 2307. Medical bound volume

Patient's history: Admitted 8/18/92; discharged 8/23/92. Age 38, male, white.

Other tuberculosis during life: Pulmonary tuberculosis.

Myocardial failure: Moderate degree with edema, liver enlargement and râles at bases of lungs.

Duration: 1 month.

Outcome: Died.

Other tuberculosis at autopsy: Chronic fibrous pleurisy. Fibrous tuberculosis of lungs. Miliary tuberculosis.

Comment: Large triangular shaped heart with absent visible or palpable impulse, and a pericardial friction rub.

Case 8. C. S., U. 6555

Patient's history: Admitted 7/29/26; discharged 8/14/26. Age 43, male, colored.

Other tuberculosis during life: Tuberculous peritonitis.

Myocardial failure: Moderate degree.

Duration: 2 months.

Outcome: Died.

Other tuberculosis at autopsy: Tuberculosis of mediastinal, cervical and mesenteric lymph nodes. Miliary tubercles in lungs, liver, spleen.

Comment: Large cardiac outline with distant sounds.

Case 9. J. B., 46139. Surgical bound volume

Patient's history: Admitted 7/17/18; discharged 8/6/18. Age 46, male, colored.

Other tuberculosis during life: Arthritis, left hip. Meningitis. Pleurisy with effusion.

Myocardial failure: None.

Outcome: Died.

Other tuberculosis at autopsy: Tuberculous arthritis, left hip. Mediastinal tuberculosis. Disseminated tubercles in lungs, liver. Tuberculous meningitis.

Comment: Large heart with poorly defined apical impulse.

Case 10. M. M., U. 21871

Patient's history: Admitted 7/22/30; discharged 8/22/30. Age 49, male, colored.

Other tuberculosis during life: Pleurisy with effusion.

Myocardial failure: Moderate degree.

Duration: 4 months.

Outcome: Died.

Other tuberculosis at autopsy: Apical scars. Mediastinal tuberculosis with extension to pleura and peritoneum.

Case 11. C. B., 28205. Medical bound volume

Patient's history: Admitted 11/14/11; discharged 12/2/11. Age 50, male, colored.

Other tuberculosis during life: Pulmonary tuberculosis.

Myocardial failure: Mild degree.

Duration: 3 months.

Outcome: Died.

Other tuberculosis at autopsy: Healing and healed pulmonary tuberculosis. Mesenteric lymphadenitis. Miliary of lungs, liver, spleen, adrenals, kidneys. Tuberculous laryngitis.

Case 12. A. B., 14027. Surgical bound volume

Patient's history: Admitted 11/7/02; discharged 12/18/02. Age 52, male, white.

Other tuberculosis during life: Bilateral psoas abscess. Tuberculous spondylitis. Para rectal abscess.

Myocardial failure: None.

Duration: 3½ months.

Outcome: Died.

Other tuberculosis at autopsy: Left lung with cavity; right lung. Mediastinal tuberculous adenitis. Para rectal tuberculous abscess. Disseminated in liver, spleen, kidneys.

Comment: Moderate pericarditis which was obscured by extensive tuberculosis elsewhere.

Case 13. W. T., 48. Medical bound volume

Patient's history: Admitted 6/27/89; discharged 7/5/89. Age 52, male, colored.

Other tuberculosis during life: None.

Myocardial failure: Marked degree with massive edema.

Duration: 2 months.

Outcome: Died.

Other tuberculosis at autopsy: Mediastinal tuberculosis. Generalized miliary tuberculosis.

Comment: Miliary tubercles were fresh and not very numerous.

Case 14. H. W., 49167. Medical bound volume

Patient's history: Admitted 4/4/23; discharged 4/7/23. Age 58, male, white.

Other tuberculosis during life: None.

Myocardial failure: Marked degree with massive edema and huge liver.

Duration: 10 months.

Outcome: Died.

Other tuberculosis at autopsy: Old apical pulmonary tubercles. Disseminated tubercles in lungs. Tuberculous enteritis. Old tubercles in spleen and liver.

Comment: Large heart with distant sounds and no murmurs. Presented picture of arteriosclerotic heart disease and myocardial failure.

Case 15. J. S., 38089. Medical bound volume

Patient's history: Admitted 6/26/17; discharged 7/10/17. Age 60, male, white.

Other tuberculosis during life: Bilateral pleurisy with effusion.

Myocardial failure: Severe cardiac failure.

Duration: 2 months.

Outcome: Died.

Other tuberculosis at autopsy: Tuberculous mediastinal lymphadenitis. Encapsulated pulmonary tuberculosis. Proliferative tuberculous pleurisy.

Comment: Large heart with distant sounds and no murmurs. Picture of arteriosclerotic heart disease with myocardial failure.

Case 16. G. F., 53537. Medical bound volume

Patient's history: Admitted 7/11/25; discharged 8/19/25. Age 70, male, colored.

Other tuberculosis during life: None.

Myocardial failure: Dyspnoea and angina pectoris.

Duration: 2 years.

Outcome: Died.

Other tuberculosis at autopsy: Mediastinal and mesenteric lymphadenitis. Caseous pneumonia, left upper lobe. Tuberculous pleura. Disseminated in liver, spleen, kidneys.

Comment: Clinically presented picture of coronary arteriosclerosis with anginal pain.

Case 17. L. A., 19371. Medical bound volume

Patient's history: Admitted 2/24/06; discharged 3/30/06. Age 74, male, white.

Other tuberculosis during life: Tuberculous bronchopneumonia.

Myocardial failure: None.

Duration: 3 months.

Outcome: Died.

Other tuberculosis at autopsy: Tuberculous bronchopneumonia. Tuberculous pleurisy. Mediastinal lymphadenitis. Tuberculous enteritis.

Comment: Large heart with distant sounds and no murmurs. Pericardial friction rub.

UNPROVEN CASES OF TUBERCULOUS PERICARDITIS

Case 1. B. R., U. 4281

Patient's history: Admitted 4/1/26; discharged 6/1/26; improved. Age 13, female, colored.

Other tuberculosis discovered during life: None.

Myocardial failure: Not present.

Amount of pericardial fluid withdrawn: No tap.

Duration of disease: 4 months.

Outcome: Well 7 years after discharge. No heart murmurs.

Comment: Heart enlarged in all diameters. Distant sounds. No murmurs. Pericardial friction present. Signs of compression of base of lung. Heart decreased in size. Sounds became louder with improvement.

Case 2. C. M., U. 55877

Patient's history: Admitted 6/5/34; discharged 7/18/34; improved. Age 14, male, colored.

Other tuberculosis discovered during life: Evidence of mediastinal tuberculosis by X-ray with calcification. Areas of calcification in the right lung by X-ray.

Myocardial failure: Not present.

Amount of pericardial fluid withdrawn: 270 cc.

Tubercle bacilli in pericardial fluid: Smear, negative. Guinea pig, negative.

Duration of disease: 2 months.

Outcome: Well 18 months after discharge.

Case 3. C. B., U. 33932

Patient's history: Admitted 11/3/30; discharged 1/11/31: died. Age 16, female, colored.

Other tuberculosis discovered during life: Bronchopneumonia (?). Patient had no sputum.

Myocardial failure: Liver enlargement. Edema. Bilateral hydrothorax. Dyspnoea. Cardiac insufficiency was progressive.

Amount of pericardial fluid withdrawn: 1,910 cc.

Tubercle bacilli in pericardial fluid: Smear, negative. Guinea pig, negative.

Duration of disease: 2½ months.

Outcome: Died. No autopsy.

Case 4. A. E., U. 23660

Patient's history: Admitted 3/14/29; discharged 4/18/29; improved. Age 16, male, white.

Other tuberculosis discovered during life: Mediastinal tuberculosis. Pleurisy with effusion.

Myocardial failure: Not present.

Amount of pericardial fluid withdrawn: No tap.

Duration of disease: 4 months.

Outcome: Improved.

Comment: No effusion. Pericardial friction rub.

Case 5. J. G., U. 36987

Patient's history: Admitted 5/8/31; discharged 6/17/31; improved. Age 18, male, colored.

Other tuberculosis discovered during life: Mediastinal tuberculosis.

Myocardial failure: Not present.

Amount of pericardial fluid withdrawn: 300 cc.

Tubercle bacilli in pericardial fluid: Smear, negative. Guinea pig, negative.

Duration of disease: 2½ months.

Outcome: Improved.

Case 6. C. H., 30681 (Medical bound volume)

Patient's history: Admitted 4/5/13; discharged 5/18/13; improved. Age 19, male, colored.

Other tuberculosis discovered during life: Bilateral pleurisy. Tuberculous arthritis, left wrist (proved by biopsy).

Myocardial failure: Ascites.

Amount of pericardial fluid withdrawn: No tap.

Duration of disease: 6 weeks.

Outcome: Improved.

Comment: Large heart with distant sounds and no murmurs. Heart gradually decreased in size. Pericardial friction rub. Paradoxical pulse. Eye test with 1 per cent tuberculin positive.

Case 7. G. A., U. 27988

Patient's history: Admitted 11/13/29; discharged 1/16/30; improved. Age 20 female, colored.

Other tuberculosis discovered during life: Mediastinal tuberculosis. Fibrosis, right upper lobe.

Myocardial failure: Slight edema.

Amount of pericardial fluid withdrawn: No tap.

Duration of disease: 3 months.

Outcome: Well after 6 years during which she has had 3 pregnancies.

Comment: Large heart with distant sounds. Pericardial friction. Paradoxical pulse. Compression of base of lung. Heart gradually became smaller. Heart now slightly enlarged. 1/100,000 tuberculin strongly positive.

Case 8. W. H., 33215 (Medical bound volume)

Patient's history: Admitted 3/2/14; discharged 3/28/14; improved. Age 20, male, colored.

Other tuberculosis discovered during life: None.

Myocardial failure: None.

Amount of pericardial fluid withdrawn: No tap.

Duration of disease: 1 month.

Outcome: Improved.

Comment: Large heart. No murmurs. Pericardial friction rub. Heart decreased in size and sounds became louder.

Case 9. A. J., U. 54788

Patient's history: Admitted 4/10/34; discharged 6/23/34; improved. Age 20, male, colored.

Other tuberculosis discovered during life: None.

Myocardial failure: Moderate cardiac insufficiency.

Amount of pericardial fluid withdrawn: 120 cc.

Duration of disease: 4½ months.

Outcome: Well 2 years after discharge.

Comment: No murmurs. Very large heart on admission, which is at present normal in size. 1/100,000 tuberculin positive.

Case 10. L. P., 50756 (Medical bound volume)

Patient's history: Admitted 2/19/24; discharged 3/5/24; improved. Age 22, male, colored.

Other tuberculosis discovered during life: Pleurisy with effusion.

Myocardial failure: None.

Amount of pericardial fluid withdrawn: No tap.

Duration of disease: 1 month.

Outcome: Improved.

Comment: Large heart with distant sounds. Pericardial friction rub. Heart gradually became smaller.

Case 11. L. R., 17239 (Medical bound volume)

Patient's history: Admitted 6/20/04; discharged 6/27/04; unimproved. Age 22, male, white.

Other tuberculosis discovered during life: None.

Myocardial failure: Large liver with mild cardiac insufficiency and slight edema.

Amount of pericardial fluid withdrawn: No tap.

Duration of disease: 1 year.

Outcome: Improved.

Comment: Large heart. Soft systolic murmur. Pericardial friction rub.

Case 12. N. R., 32158 (Medical bound volume)

Patient's history: Admitted 2/18/14; discharged 4/16/14; improved. Age 23, male, colored.

Other tuberculosis discovered during life: Cervical adenitis with sinus tract. Pleurisy.

Myocardial failure: None.

Amount of pericardial fluid withdrawn: No tap.

Duration of disease: 3 months.

Outcome: Improved.

Comment: Large heart with distant sounds and no murmurs. Pericardial friction rub. Calmette 1 per cent positive.

Case 13. R. J., U. 25007

Patient's history: Admitted 5/31/29; discharged 9/11/29; improved. Age 24, male, colored.

Other tuberculosis discovered during life: Mediastinal tuberculosis.

Myocardial failure: None.

Amount of pericardial fluid withdrawn: No tap.

Duration of disease: 8 months.

Outcome: Improved.

Comment: Large heart with pericardial friction rub. Heart gradually became smaller. 1/10,000 tuberculin positive.

Case 14. J. P., 9568. Medical bound volume

Patient's history: Admitted 4/3/94; discharged 5/21/94; improved. Age 24, male, colored.

Other tuberculosis discovered during life: None.

Myocardial failure: Mild cardiac insufficiency.

Amount of pericardial fluid withdrawn: No tap.

Duration of disease: 8 months.

Outcome: Improved.

Comment: Large heart with distant sounds and no visible impulse. No murmurs. Pericardial friction rub.

Case 15. C. R., U. 35547

Patient's history: Admitted 2/13/31; discharged 3/27/31; improved. Age 25, male, colored.

Other tuberculosis discovered during life: Pleurisy with effusion.

Myocardial failure: None.

Amount of pericardial fluid withdrawn: 800 cc.

Tubercle bacilli in pericardial fluid: Smear, negative. Guinea pig, negative.

Duration of disease: 6 weeks.

Outcome: Improved. Well after discharge.

Case 16. S. W., U. 62766

Patient's history: Admitted 5/31/35; discharged 8/1/35; improved. Age 25, male, colored.

Other tuberculosis discovered during life: Pleurisy, right. Tuberculous mediastinal adenitis. Extradural tuberculoma (proven by guinea pig inoculation).

Myocardial failure: Mild cardiac insufficiency.

Amount of pericardial fluid withdrawn: 1,000 cc.

Tubercle bacilli in pericardial fluid: Smear, negative. Guinea pig, negative.

Duration of disease: 2 months.

Outcome: One year after discharge heart slightly enlarged.

Comment: Returned 3/18/36 with an epidural tuberculoma which was removed by operation.

Case 17. W. H.

Patient's history: Admitted 10/1/99; discharged 11/1/99; improved. Age 26, male, white.

Other tuberculosis discovered during life: Past history of pleurisy with effusion. Apical tuberculosis. Tuberculous laryngitis.

Myocardial failure: Mild cardiac insufficiency.

Amount of pericardial fluid withdrawn: 1,250 cc.

Tubercle bacilli in pericardial fluid: Smear, negative. Guinea pig, negative.

Duration of disease: 6 weeks.

Outcome: Four years after discharge pulmonary and laryngeal tuberculosis.

Comment: Four years after discharge signs of adherent pericardium without cardiac failure were present.

Case 18. F. R., 18751. Medical bound volume

Patient's history: Admitted 8/14/05; discharged 10/12/05; improved. Age 26, male, white.

Other tuberculosis discovered during life: ? Apical, right lung. ? Peritonitis.

Myocardial failure: Slight.

Amount of pericardial fluid withdrawn: No tap.

Duration of disease: 2½ months.

Outcome: Seven years after discharge he had marked portal obstruction and signs of adhesive mediastinitis.

Comment: Large heart with distant sounds and pericardial friction rub. Friction rub over liver. Heart became smaller.

Case 19. G. K., 41871. Medical bound volume

Patient's history: Admitted 3/26/19; discharged 5/31/19; died. Age 28, male, colored.

Other tuberculosis discovered during life: Bilateral pleurisy with effusion.

Myocardial failure: Severe failure which progressed until death.

Amount of pericardial fluid withdrawn: No tap.

Duration of disease: 7 months.

Outcome: Died. No autopsy.

Comment: Signs of a large pericardial effusion. No murmurs.

Case 20. S. T., U. 58193

Patient's history: Admitted 5/9/32; discharged 9/24/32; improved. Age 28, female, colored.

Other tuberculosis discovered during life: Bilateral pleural effusion.

Myocardial failure: Mild cardiac insufficiency.

Duration of disease: 5 months.

Outcome: Well 2½ years after discharge.

Comment: Signs of a moderate sized pericardial effusion. Heart became smaller as patient improved. Tuberculin (0.1 mgm.) positive (strongly).

Case 21. C. T., U. 60568

Patient's history: Admitted 2/9/35; discharged 5/22/35; improved. Age 28, males colored.

Other tuberculosis discovered during life: Mediastinal tuberculosis.

Myocardial failure: None.

Amount of pericardial fluid withdrawn: 280 cc.

Tubercle bacilli in pericardial fluid: Smear, negative. Guinea pig, negative.

Duration of disease: 5 months.

Outcome: Well 1 year after discharge.

Comment: Tuberculin 1/10,000 positive.

Case 22. D. D., 46270. Medical bound volume

Patient's history: Admitted 10/17/21; discharged 10/21/21. Age 29, male, colored.

Other tuberculosis discovered during life: Pleurisy with effusion.

Myocardial failure: None.

Amount of pericardial fluid withdrawn: No tap.

Duration of disease: 2 months.

Outcome: Not treated.

Comment: Not treated. Fibrinous pericarditis.

Case 23. W. L., 38567. Medical bound volume

Patient's history: Admitted 10/1/17; discharged 10/17/17; improved. Age 33, male, colored.

Other tuberculosis discovered during life: None.

Myocardial failure: None.

Amount of pericardial fluid withdrawn: No tap.

Duration of disease: 1 month.

Outcome: Improved.

Comment: Moderate sized pericardial effusion. Heart gradually became normal in size.

Case 24. A. J., U. 37940

Patient's history: Admitted 7/3/31; discharged 7/16/31; improved. Age 38, male, colored.

Other tuberculosis discovered during life: ? Peritonitis. Pleurisy with effusion, right.

Myocardial failure: Mild degree.

Amount of pericardial fluid withdrawn: 1,855 cc.

Tubercle bacilli in pericardial fluid: Smear, negative. Guinea pig, negative.

Duration of disease: 5 months.

Outcome: Improved.

Comment: No follow-up.

Case 25. C. B., U. 40374

Patient's history: Admitted 11/25/31; discharged 1/21/32; improved. Age 42, male, white.

Other tuberculosis discovered during life: None.

Myocardial failure: None.

Amount of pericardial fluid withdrawn: No tap.

Duration of disease: 2½ months.

Outcome: Well 5 years after discharge.

Comment: Large heart with pericardial friction rub and enlarged liver. Heart gradually became normal in size. Tuberculin 1/10,000 positive.

Case 26. J. D., 31742. Medical bound volume

Patient's history: Admitted 11/20/13; discharged 1/12/14; improved. Age 42, male, colored.

Other tuberculosis discovered during life: Bilateral apical tuberculosis.

Myocardial failure: Moderate degree.

Amount of pericardial fluid withdrawn: No tap.

Duration of disease: 2 months.

Outcome: Improved.

Comment: Signs of a moderate sized pericardial effusion with a pericardial friction rub.

Case 27. J. J., U. 57202

Patient's history: Admitted 9/10/34; discharged 11/20/34; improved. Age 42, male, colored.

Other tuberculosis discovered during life: Old apical tuberculosis.

Myocardial failure: None.

Amount of pericardial fluid withdrawn: No tap.

Duration of disease: 3½ months.

Outcome: Well 1½ years after discharge.

Comment: Large heart with distant sounds and no murmurs. Pericardial friction rub present. Heart gradually diminished in size. Tuberculin 1/10,000 positive.

Case 28. M. C., 16964. Medical bound volume

Patient's history: Admitted 4/12/04; discharged 5/31/04; unimproved. Age 43, male, white.

Other tuberculosis discovered during life: None.

Myocardial failure: Moderate degree with ascites. Large liver.

Amount of pericardial fluid withdrawn: No tap.

Duration of disease: 2 years.

Outcome: Unimproved.

Comment: Huge heart with faint sounds and no murmurs. Pericardial friction rub present. Discharged unimproved with signs unchanged. One tubercle bacillus found in sputum (?).

Case 29. B. S., U. 25484

Patient's history: Admitted 6/28/29; discharged 9/21/29; improved. Age 45, female, colored.

Other tuberculosis discovered during life: Bilateral fibrinous pleurisy. Fibrosis at right apex.

Myocardial failure: None.

Amount of pericardial fluid withdrawn: No tap.

Duration of disease: 2 months.

Outcome: Improved.

Comment: Large heart with progressively diminishing sounds and development of a pericardial friction rub. Heart gradually became smaller and sounds became louder.

Case 30. S. C., 32579. Medical bound volume

Patient's history: Admitted 5/12/14; discharged 5/27/14; improved. Age 46, male, colored.

Other tuberculosis discovered during life: None.

Myocardial failure: None.

Amount of pericardial fluid withdrawn: No tap.

Duration of disease: 2 months.

Outcome: Improved.

Comment: Large heart with distant sounds and no murmurs. Pericardial friction rub present. Improved. Calmette test 1 per cent positive.

Case 31. M. D., 24423. Medical bound volume

Patient's history: Admitted 8/10/08; discharged 9/3/08; improved. Age 47, female, white.

Other tuberculosis discovered during life: None.

Myocardial failure: Moderate degree which increased and later subsided.

Amount of pericardial fluid withdrawn: No tap.

Duration of disease: 2 months.

Outcome: Improved.

Comment: Signs of a large pericardial effusion.

Case 32. J. M., 33843. Medical bound volume

Patient's history: Admitted 3/9/15; discharged 4/1/15; improved. Age 48, male, white.

Other tuberculosis discovered during life: Pulmonary tuberculosis. Pleurisy with effusion, right.

Myocardial failure: Moderate degree.

Amount of pericardial fluid withdrawn: 1,200 cc.

Duration of disease: Almost 1 year.

Outcome: Improved.

Comment: Calmette test 1 per cent positive.

Case 33. C. B., U. 61044

Patient's history: Admitted 3/6/35; discharged 5/30/35; improved. Age 55, male, colored.

Other tuberculosis discovered during life: Tuberculous mediastinal nodes. Cold abscess over precordium (proved by guinea pig inoculation).

Myocardial failure: Mild degree.

Amount of pericardial fluid withdrawn: No tap.

Duration of disease: 3 months.

Outcome: Improved.

Comment: Signs of large effusion which cleared up. He came back 6 months later with a cold abscess in 4th interspace to left of sternum.

Case 34. H. C., U. 51556

Patient's history: Admitted 10/3/33; discharged 1/9/34; improved. Age 60, male, colored.

Other tuberculosis discovered during life: Mediastinal tuberculosis.

Myocardial failure: Moderate degree.

Amount of pericardial fluid withdrawn: 1,710 cc.

Tubercle bacilli in pericardial fluid: Smear, negative. Guinea pig, negative.

Duration of disease: 3½ months.

Outcome: Well 2½ years after discharge.

Comment: Now has signs of adhesive mediastinitis without any symptoms. Tuberculin 1/100,000 positive.

RECENT ADVANCES IN THE BLOOD COAGULATION PROBLEM[1]

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I. INTRODUCTION

A number of theories have been suggested as to the mechanism of the coagulation phenomenon. Some of these are summarized in highly condensed form in table I; a more elaborate description may be found in a series of recent reviews by Morawitz (110), Fonio (40), Fuchs (47), Wöhlisch (152), Zunz (159), and Howell (78). The review by Wöhlisch is particularly complete.

The very fact that there are now so many contradictory and mutually exclusive theories implies that the experimental data on which they are based are either in error or incomplete. Not infrequently, substances have been hypothesized to explain a given phenomenon when the only evidence for the existence of these substances is the phenomenon itself. Many of the terms applied to the several reagents imply a function which is still debatable; and numerous workers have chosen to apply wholly dissimilar terms to the same reagent. The result is a terminology which is the despair of the student and investigator alike (cf. table I).

The most promising approach would accordingly seem to be a return to first principles; and in so doing we must not only discard a cumbersome and confusing terminology, but must hold definitive, rigid theories in abeyance. The immediate problem is not one of a satisfactory theory, but of new methods of experimental attack.

The purpose of the present paper is accordingly twofold. In the first place, an attempt is made to consider critically the actual experimental data, and to identify those few observations concerning which most investigators are in essential agreement, as distinguished from

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[1] The 1936 Alvarenga Prize Essay (College of Physicians, Philadelphia).

TABLE I

*Some of the Theories as to the Mechanism of Coagulation**

AUTHOR†	ACTIVE PARTICIPANTS IN THE PROCESS IN ADDITION TO FIBRINOGEN AND CALCIUM‡		INHIBITORY FACTORS	SUPPOSED SEQUENCE OF EVENTS
	Plasma factor	Platelet or tissue factor		
Thrombin Theories of Coagulation				
Schmidt (134, 135) 1872; 1893	Prothrombin	Thromboplastin Zymoplastic substance	"Cytoglobin," and antithrombin	Prothrombin + zymoplastic substance → thrombin Thrombin + "fibrinoplastic substance" + fibrinogen → fibrin
Hammarsten (57, 58) 1880–1898				$\longrightarrow$ thrombin Thrombin + fibrinogen → fibrin
Morawitz (108) 1904	Thrombogen	Thrombokinase	Antithrombin	Thrombokinase + thrombogen + Ca → thrombin Thrombin + fibrinogen → fibrin
Fuld and Spiro (51) 1904	Plasmozyme	Cytozyme		Thrombin + fibrinogen → fibrin
Mellanby (93) 1909 Pickering (121, 122) 1921–1928	Prothrombin		An unidentified inhibitory factor stabilizing a prothrombin	Stabilizing factor is somehow destroyed *in vitro*, allowing calcium to activate prothrombin-fibrinogen complex to form fibrin.
Bordet (9, 10, 11) 1912–1920	Proserozyme	Cytozyme	A plasma inhibitor affecting serozyme	Proserozyme $\xrightarrow[\text{contact}]{\text{calcium}}$ serozyme Serozyme + cytozyme + calcium → thrombin

Howell (70–80) 1910–1935 Fuchs (42–44) 1930	Prothrombin	Thromboplastin Cephalin	Antithrombin Antiprothrombin (heparin) Pro-antithrombin	Prothrombin-antiprothrombin + cephalin → prothrombin + cephalin-antiprothrombin Prothrombin + calcium → thrombin Thrombin + fibrinogen → fibrin
Non-Thrombin Theories				
Wooldridge (155, 156) 1886	Fibrinogen B	Tissue fibrinogen (Fibrinogen A)		Blood fibrinogen + tissue fibrinogen → fibrin + thrombin
Nolf (114–117) 1905–1913	Thrombogen	Thrombozyme		Thrombozyme + thrombogen + calcium + fibrinogen → fibrin + thrombin
Mills (99, 101–105) 1921–1927	Blood fibrinogen	Tissue fibrinogen		Blood fibrinogen + tissue fibrinogen + calcium → fibrin
Stuber (141, 142) 1923–1930	Glucose			Glucose → lactic acid Acid + fibrinogen → fibrin
Hekma (65, 65a) 1914–1929				a. Fibrinogen $\underset{\text{base}}{\overset{\text{acid}}{\rightleftarrows}}$ fibrin b. Fibrin = fibrinogen "agglutinated" by thrombin

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* Cf. Eagle (23).

† For general reviews see Fonio (40), Howell (75, 77, 78), Morawitz (110), Pickering (122), Wöhlisch (152), Fuchs (47) and Zunz (159).

‡ The essential rôle of calcium in coagulation was first recognized by Arthus and Pages.

those which are still in question. In the second place, certain recent studies are summarized which do offer a fresh experimental approach to this perplexing problem, unencumbered by a confusing terminology or an involved superstructure of theory.[2]

It has been found convenient to divide the following discussion into three headings: (1) the mechanism of blood coagulation *in vitro*; (2) the reason for its failure to occur *in vivo*; and (3) clinical aspects of the blood coagulation phenomenon.

II. THE COAGULATION OF SHED BLOOD[2]

A. Coagulation as a Biphasic Reaction

The elementary facts of coagulation, established by Schmidt (134, 135), Hammarsten (57, 58) and Morawitz (108–110) are these: the plasma of circulating blood contains a labile protein, *fibrinogen*. When blood is shed this protein forms a gel-like structure, a coagulum of *fibrin*, in the interstices of which the cells and serum are enmeshed to form an elastic structure, the blood clot. The serum may be subsequently expressed from the clot, and differs from plasma in the fact that it contains no fibrinogen, and does contain an active coagulant, *thrombin*, apparently released during the process of coagulation. By virtue of this coagulant, fresh serum will clot either purified solutions of fibrinogen, or plasma prevented from coagulating spontaneously by the addition of some one of the anticoagulants to be later discussed.

To these early investigators, and to most of those who have since studied the problem, it seemed natural to believe that coagulation involved two distinct and consecutive reactions: the first was the formation of thrombin from its precursors in the circulating blood; and the second was the interaction between thrombin and fibrinogen to form fibrin. From time to time, however, it has been suggested that thrombin plays no part in physiological coagulation, but is merely a by-product which is not causally related to the observed phenomenon.

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[2] There have been omitted from consideration here the numerous papers in which various chemicals have been reported to accelerate or retard coagulation. As will appear, fibrin formation involves at least five reagents and at least two consecutive reactions. The experimental finding that a given agent accelerates or retards coagulation raises the immediate question as to which factor or which part reaction is being affected, and per se adds but little to our understanding of the coagulation phenomenon.

1. Thus, Nolf (115–117) suggested that fibrinogen, a hypothetical protein "thrombogen," and "thrombozyme," a hypothetical enzyme derived from white blood cells and the walls of blood vessels, interact to form fibrin and thrombin, and that thrombin is a *result* of coagulation rather than its cause. His theory includes numerous bizarre relationships between the reagents for which later investigators can find no confirmation. The fundamental thesis that thrombin formation follows coagulation is contradicted by the fact, first, that thrombin can be formed in the complete absence of fibrinogen (10) (11) (23) (95) (96); second, that those factors which accelerate thrombin production likewise accelerate coagulation; and third, that coagulation immediately follows the almost explosive liberation of large amounts of the active coagulant, thrombin.

2. More recently, Mills and his coworkers (102–105) have suggested that there are two types of blood coagulation. They grant that in the test tube thrombin is first formed and reacts with fibrinogen to form fibrin. In wounds, however, they believe that there is an entirely different mechanism, similar to a theory proposed by Wooldridge (156). A tissue factor which they term "tissue fibrinogen" presumably combines directly with fibrinogen and calcium to form the actual clot. They consider this to be a strictly stoichiometric combination: the "tissue fibrinogen" is identified as a protein nucleus with multiple phosphatide groups, each of which presumably combines with a molecule of blood fibrinogen by means of a calcium link to form fibrin.

The chemical evidence that such a compound actually forms is far from convincing. Aside from this, however, the validity of the theory rests on two major observations, and neither of these is adequate. The mere fact that tissue extract added to plasma increases the actual weight of the clot by as much as 150 per cent hardly suffices to prove chemical combination, since many colloids are similarly adsorbed by fibrin clots (102). In the second place, Mills and his coworkers claim that their tissue extracts can clot purified fibrinogen, which would clearly exclude the participation of thrombin. Other investigators, however, (9–11) (51) (108–110) (123a) (133) (137) (152); have found that purified fibrinogen, or plasma freed from the precursors of thrombin, are not coagulated by tissue or platelet derivatives and calcium. The available evidence clearly does not justify the postulation of two dissimilar mechanisms of blood coagulation.

3. The numerous publications of Stuber and his coworkers (141), who ascribe the coagulation of blood to glycolysis, and a resultant increase in acidity, have not been confirmed. Hartmann and Kühnau (62) find no correlation between glycolysis and coagulation: one may observe coagulation in the absence of any demonstrable glycolysis, and active glycolysis without coagulation. Moreover, the complete removal of glucose, as by dialysis, does not prevent coagulation. These findings have been confirmed in this laboratory. Indeed, even on *a priori* grounds, the theory is improbable. The transformation of all the blood glucose (80 mgm. per cent, or M/2250) to lactic acid would not effect a sufficient shift in the pH of the blood to precipitate fibrinogen. Moreover, recent work indicates that there is no demonstrable change in the pH of blood during coagulation (27, 38).

4. Hekma (65) in an interesting series of papers has attempted to establish the thesis that the transformation of fibrinogen to fibrin is a reversible sol-gel transformation. On this theory, fibrinogen is the alkaline hydrosol of fibrin, and is regenerated when fibrin is dissolved in alkali. However, as was shown by Barkan and Gaspar (3a) and Wöhlisch (152, p. 547) and confirmed in this laboratory, an alkaline solution of fibrin is not fibrinogen, insofar as it is not coagulated by thrombin. Moreover, the coagulation of fibrinogen does not necessarily involve a change in hydrogen ion concentration (27, 38). Finally, as Wöhlisch (l.c.) has pointed out, the isoelectric precipitation of fibrinogen is a reversible reaction which does not lead to the formation of a gel, and in both respects differs fundamentally from the physiological formation of fibrin.

Thus, none of the theories of coagulation which would deny the participation of thrombin bears critical examination. Since the burden of proof rests with those who would deny what seems to be a self-evident causal relationship between thrombin and coagulation, since the experimental data on which these non-thrombin theories are based have not been confirmed, and since the known facts of the kinetics of coagulation are wholly consistent with the thesis that thrombin is the actual coagulant, it seems fair to conclude that, as was clearly formulated by Morawitz and by Fuld and Spiro in 1904, coagulation involves two consecutive reactions. The first is the complicated sequence of events which leads to the formation of thrombin, and the second is the interaction between thrombin and fibrinogen to form fibrin.

B. The Formation of Thrombin from Its Precursors in the Circulating Blood

The majority of workers are agreed that at least three reagents play a part in the formation of thrombin. As was shown by Morawitz (108) and by Fuld and Spiro (51) in 1904, and has been repeatedly confirmed since (9–11) (23) (42, 44, 47) (95, 96) (70–72) (152), thrombin is formed by the interaction of (1) calcium ions, (2) a plasma factor, and (3) a substance derived from blood platelets, which can be replaced by tissue extracts, and which may be present in traces in cell-free plasma. As will be presently discussed, the name "*prothrombin*" originally applied to the plasma factor by Schmidt (135) correctly describes its probable function, and will therefore be used throughout this paper. On the other hand, the various terms suggested for the platelet or tissue derivative (thrombozyme, cytozyme, thromboplastin, thrombokinase) all imply functions which are still debatable. It will therefore simply be termed *tissue* or *platelet derivative* in the following pages. The little that is known concerning the properties of these two factors can be readily summarized.

1. *Prothrombin.* The plasma factor is associated with the proteins, is destroyed by trypsin (28), and is adsorbed by either tricalcium phosphate (9, 10) (51a) or magnesium or aluminium (43) hydroxide. It can be recovered from these adsorbents by dissolving the precipitate suspension with CO_2. The identification of prothrombin with complement midpiece by Fuchs and Falkenhausen (46, 48), is probably in error (7) (23) (123).

Aside from the constant association of prothrombin with plasma globulin, little is known of its chemical properties. A considerable portion is precipitated on the weak acidification of plasma previously diluted with ten or fifteen volumes of cold water. Thus, Mellanby (95) adds acetic acid to approximately pH 5.0, and Eagle (23) bubbles CO_2 through the water-diluted plasma. The method of preparation which yields the purest prothrombin, i.e., containing most active substance per unit protein, is probably that of Mellanby, who extracts the acetic acid precipitate with a dilute solution of $Ca(HCO_3)_2$. This dissolves out prothrombin preferentially, and leaves behind the bulk of the inert globulin and almost all of the fibrinogen carried down in the original crude precipitate. The solution may be further purified by re-precipitating at pH 5.0.

2. *Tissue or platelet derivative.* Given such a solution of comparatively purified prothrombin, the addition of $CaCl_2$ either has no effect, or causes the slow formation of small amounts of the active coagulant, thrombin. If however, one adds to this prothrombin-calcium mixture a minute quantity of a washed platelet suspension, there is a prompt evolution of comparatively large quantities of thrombin. Indeed, if citrated plasma is merely passed through a Berkefeld filter to remove all cellular material and then recalcified, it frequently fails to clot unless platelets are restored (Cramer and Pringle (18)). Even when the filtered plasma does clot, the coagulation time is markedly prolonged. In view of the traces of platelet material required, coagulation in such cases may perhaps be due to the release into solution of sufficient platelet substance to cause the generation of thrombin.

Clearly, the platelets provide something essential for the coagulation of blood. Almost any aqueous tissue extract can replace the platelets in this respect. Until satisfactory evidence has been presented to the contrary, we may therefore proceed under the assumption that platelets and tissue extracts supply the same essential reagent. Red blood cells (131) (155) and milk (82) (138) have also been reported to contain this same factor. Several investigators (5) (37b) (42) (108a) (133) report that platelets contain not only this tissue factor, but prothrombin as well: in other words, that platelets and calcium suffice for the production of thrombin. However, both Bordet (11) and Mills (99) dispute this observation; and Eagle (23) has found that even a thousand-fold excess of platelets does not affect the amount of thrombin formed. This implies that platelets contain no significant amount of prothrombin.

The origin of platelets within the body is still debatable. There is some evidence that they are derived from megakaryocytes; and Howell (78a) has recently presented evidence that they are liberated in large quantity in the lung.

Considerable work has been done in an attempt to identify the material supplied by platelets and tissue extracts. It has been amply demonstrated that lipoid solvents such as alcohol, ether or petroleum ether, will extract a thermostable substance from either platelets or tissues which is an adequate substitute for these materials in initiating the production of thrombin. Zak (158) and Bordet (11) both identified this substance as a lecithin; while Howell (72), and many later investigators (55) (101) (92) have found lecithin to be inactive, and ascribe the coagulating activity of these lipoidal extracts to their cephalin content. Still more recently, Fischer and Hecht (39), and Charles, Fisher and Scott (15) claim that the active material is not cephalin, but some other as yet unidentified substance.

It must be borne in mind that these lipoidal extracts are not nearly as active as the corresponding crude aqueous tissue extracts or platelet suspension (72) (130a) (160), which suggests that the active coagulant may be either some as yet unidentified substance which is removed by lipoid solvents only in part, *or* some complex molecule such as lipoprotein which is far more active than its lipoid component. This possibility assumed particular significance in the light of the data to be discussed on page 108.

3. *Calcium.*[3] It is clearly established (3) that calcium ions are essential for physiological coagulation. Blood to which citrate, fluoride or oxalate has been added fails to coagulate. The first two salts form a non-ionized complex ion with calcium, and the last named forms an insoluble salt. Attempts by Vines (148) to show that a complex calcium compound rather than the simple ion is the actual coagulant are apparently disproved by Wöhlisch and Paschkis (154). The suggestion by Stuber and Sano (142) that citrate and oxalate prevent coagulation by a direct action on fibrinogen is likewise in contradiction with often repeated experimental findings (cf. Wöhlisch (152), p. 489).

4. *The interaction between calcium, platelet (or tissue) derivative and prothrombin.* Given these three reagents, how do they interact to form thrombin? Morawitz (108–110) is prominently identified with the theory that the platelet factor is an enzyme (thrombokinase) which promotes the formation of thrombin. As suggested by Bordet (9–11), and again by Fischer (38a), by Fuchs (42–44, 47), and by Mills (99) (100) (101), the 3 reagents actually combine chemically: that is,

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[3] The literature as to the rôle of calcium in coagulation has recently been critically reviewed by Ferguson (37a).

thrombin is a prothrombin-calcium-platelet compound. According to Herzfeld and Klinger (66), Pickering (121) (122), and Howell (71, 75, 77, 78) thrombin is simply a calcium-prothrombin compound. The latter investigator and also Fuchs (47) believe that the platelets serve to break the prothrombin loose from its combination with a hypothetical inhibitor (heparin) (cf. page 117). Pickering (121, 122) and Hekma (65) believe that the platelets break prothrombin from a hypothetical combination with other plasma proteins (cf. page 116).

Obviously, these theories as to the nature of the reaction between calcium, prothrombin and platelets cannot all be correct, and the evidence for most, if not all, seems inadequate. It is significant that the amount of thrombin ultimately formed in a calcium-prothrombin-platelet mixture is independent of the amount of platelets, cephalin or tissue extractive used in excess of the minimum effective concentration (23). Over a wide range of concentrations, these merely *accelerate* the formation of thrombin in proportion to the amount used; but a minute quantity suffices to cause a slow but progressive evolution of thrombin, which eventually may equal the amount produced in mixtures containing one thousand times as many platelets. On the other hand, if the platelets are kept constant, and the amount of prothrombin varied, it is found that the amount of thrombin produced varies directly with the amount of prothrombin used. Moreover, contrary to Loucks and Scott (89), and confirming Hammarsten (57, 58) calcium can be precipitated quantitatively from the final thrombin preparations as the oxalate, without affecting their coagulating activity (24) (152). A large excess of citrate or oxalate is, however, reported to inhibit thrombin activity (cf. 37a).

Given these three observations: (1) that thrombin can be prepared containing no analytically demonstrable calcium; (2) that a certain minimum quantity of platelets (or tissue extractive) is necessary for the activation of prothrombin to thrombin; and (3) that the amount of thrombin formed is largely independent of the amount of platelets used in excess of this necessary minimum, but varies directly with the amount of prothrombin used, two possible explanations suggest themselves. Calcium and platelets may not be an intrinsic part of thrombin, but may merely activate prothrombin to thrombin, as was implied by Morawitz (108) when he termed the platelet factor thrombokinase.

The spontaneous activation of prothrombin to thrombin noted by Mellanby (96) and Cekada (13), and its activation by chloroform, ethyl alcohol and carbon tetrachloride, as reported by Cekada (13), would, if confirmed, lend further support to this theory. On the other hand, it is conceivable that thrombin may be a true prothrombin-calcium-platelet compound present in such minute molecular concentration in the ordinary thrombin solutions that the amount of calcium would not be analytically demonstrable, and the amount of platelets required would be vanishingly small. Thus, it is not improbable that in the thrombin solutions prepared by the Eagle or Mellanby technic, which contain on the order of 0.05 to 0.15 per cent protein, the active constituent is present in a concentration of 0.010 per cent, or less. If we assume the thrombin to be a protein and assign an arbitrary value of 100,000 for its molecular weight, this concentration is approximately a 1/1,000,000 molar solution. The mere fact that calcium cannot be demonstrated analytically does not exclude its being a component part of the thrombin molecule.[4]

Similarly, the fact that thrombin has been prepared containing no demonstrable phosphorus (13) (77) does not per se exclude the possibility that platelets or tissue derivatives are a part of the thrombin molecule. Even if we assume (unjustifiably) that prothrombin as such is phosphorus-free, and that the tissue derivative is a phosphatide, the presence of 1/1,000,000 molar phosphorus, or 0.00004 mgm. per cubic centimeter, would probably not have been detected by the methods employed.

In summary, the data previously cited do not justify any definite decision as to the nature of the calcium-platelet-prothrombin reaction. The question must be reinvestigated in the light of the recent finding (26, 28) that trypsin and certain proteolytic snake venoms activate prothrombin to thrombin.

It has been known for many years that trypsin added to blood accelerated its spontaneous coagulation. This phenomenon was first noted by Douglas and Colebrook (20) in 1916 and was apparently rediscovered by Waldschmidt-Leitz and coworkers (150) in 1929. No attention was paid to an obscure report by Heard (64) in 1917 that trypsin could coagulate oxalated blood; and Mellanby (97a), on repeating Heard's work in 1935, concluded that the supposed coagulation by trypsin was actually due to calcium impurities in the enzyme preparations, and not due to the enzyme as such.

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[4] The possibility that thrombin as formed physiologically contains calcium as an intrinsic part of the molecule is supported by the following observations. Electrodialyzed thrombin has been reported to be inactive unless a trace of calcium is added (126). Similarly, a large excess of oxalate or citrate has been reported to cause a definite impairment of thrombin activity (37a). Nevertheless, as is developed in the following pages, thrombin *can* be prepared in the complete absence of ionized calcium by the action of trypsin and of snake venoms on prothrombin.

A chance observation in this laboratory led to the discovery that trypsin caused the coagulation of citrated plasma. Further study of the phenomenon revealed that calcium played no part in the reaction, for it was observed with dialyzed trypsin and strongly citrated plasma; and the participation of calcium was apparently excluded by using crystalline trypsin prepared by Northrop and Kunitz (85). Such crystalline trypsin, per unit weight, was 80 to 120 times more effective in causing coagulation than the crude pancreatic preparation. The preparation of crystalline trypsin contains $MgSO_4$, which might conceivably function as the $CaCl_2$: but this possibility was excluded by the fact that $MgSO_4$ had no effect on the plasma, and that after dialysis of the enzyme until it contained no demonstrable SO_4 ion, it had quantitatively its original coagulating action (28).

On attempting to ascertain the mechanism of this coagulation, it was found that trypsin in any concentration did not affect the coagulation of fibrinogen, and an excess merely digested the latter, rendering it incapable of coagulation by subsequently added thrombin. Instead, it was found that trypsin converts prothrombin to thrombin. This reaction takes place over a relatively narrow optimum range of trypsin concentration, determined by the protein content of the prothrombin solution. With too much trypsin, prothrombin and thrombin are both destroyed, and with too little there is no significant effect. The evolution of thrombin is fairly rapid, and as in the case of calcium and platelets, soon reaches a maximum level at which it may remain for several hours. Again resembling the activation of prothrombin by platelets and calcium, there is a linear correlation between the amount of prothrombin used and the amount of thrombin formed at the optimal trypsin-prothrombin ratio. Finally, trypsin injected intravenously into rabbits in the amount calculated to produce coagulation of the circulating blood caused death of the animals within 2 minutes; and on immediate autopsy soft clots were found in the heart and large vessels, and the surrounding blood was found to contain no fibrinogen.

It was subsequently found (26) that certain snake venoms, known to contain proteolytic enzymes, and known to cause the coagulation of blood or plasma, transform prothrombin to thrombin. In the case of at least three venoms (Notechis scutatus, the Australian tiger snake; Bothrops atrox, the fer-de-lance; Bothrops jararaca, the jararaca snake) the crude venoms were found to be effective in extraordinarily high dilution, often exceeding 1:1,000,000. As in the case of the physiological calcium-platelet system, increasing the venom even a thousand fold beyond the amount necessary for complete activation of the prothrombin merely increased the rate of thrombin production, but not the amount ultimately formed. The latter depends primarily on the amount of prothrombin used. Clearly, the venoms somehow activate the prothrombin. Because of the minute concentrations of venom found effective; because the course of the activation resembles that of the activation of trypsinogen by enterokinase, or of chymotrypsinogen by trypsin (85); because of the considerable evidence which indicates that prothrombin is a protein; and because of a partial correlation between the proteolytic activity of the several venoms as measured with gelatin and their activity in converting prothrombin to thrombin, it was suggested as a working hypothesis that these venoms, like trypsin, convert prothrombin to thrombin by virtue of their proteolytic enzyme content (26).

The activation of prothrombin by trypsin (or venom) proceeds in the absence of calcium, and is likewise independent of the presence or absence of either platelets or tissue derivative. The proteolytic enzymes thus accomplish what is normally effected by platelets plus calcium. It is particularly significant that if one follows the rate at which thrombin is elaborated from prothrombin under the influence of the calcium-platelet system (23) (94a), snake venoms (26), or crystalline trypsin (28), one obtains quite similar curves. An initial latent period during which there is no demonstrable formation of thrombin is followed by an autocatalytic type of curve. The greater the concentration of the activating factor, the shorter is this latent period.

It is difficult to conceive of so specific a change as the conversion of prothrombin to thrombin being effected by two wholly dissimilar mechanisms. It therefore seems an entirely plausible thesis that a platelet (tissue) derivative and calcium together constitute a proteolytic enzyme which, like trypsin and certain proteolytic snake venoms, reacts with prothrombin to form thrombin, and that this is their normal rôle in the coagulation process. Except for the disputed observation that cephalin *per se* is an adequate substitute for tissue or platelet derivatives, the known facts concerning the activation of prothrombin to thrombin are entirely consistent with this hypothesis.[5]

C. The Reaction Between Thrombin and Fibrinogen to Form Fibrin

1. *Thrombin.* As in the case of prothrombin, little has been added to our knowledge of the chemical nature of thrombin. The data cited in the preceding section indicate that it may be a hydrolysis product of prothrombin. Like the latter, it resembles protein in its chemical and physical properties. Mellanby (96) finds thrombin to be of smaller molecular size than prothrombin, as judged by its diffusibility through cellophane. This important observation has not been confirmed. The question as to whether thrombin as formed physiologically contains calcium has been previously discussed.

The simplest method of preparing thrombin is to add calcium to the precipitate obtained on the weak acidification of water-diluted plasma (23) (95) (cf. page 101). The purest thrombin available, i.e., with the greatest activity per unit protein, is probably that obtained on adding calcium and tissue extract to purified prothrombin as prepared by Mellanby's technic (95) (96).

2. *Fibrinogen.* A very significant recent contribution to the chemistry of fibrinogen is the finding (8a, 153) that its solutions exhibit the phenomenon of double refraction of flow. The molecular orientation so indicated may be related to their tendency to "crystallize" as long needles of fibrin under the influence of thrombin.

3. *The formation of fibrin.* The nature of the reaction between

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[5] The observation that certain bacteria, notably Staphylococcus aureus, may cause the coagulation of citrated or oxalated blood or plasma (54, 56, 149) may well be due to the release by these bacteria of proteolytic enzymes, which, like trypsin, certain snake venoms, or the calcium-platelet system, activate prothrombin to thrombin. It is also possible that the bacterial enzyme, like papain and some snake venoms, acts directly on fibrinogen to form fibrin. These two possibilities are now being investigated in this laboratory.

thrombin and fibrinogen to form fibrin is still largely speculative. The theory of Hekma (65a) that thrombin is simply an agglutinin and dehydrating agent for submicroscopic particles of fibrinogen is wholly unsupported by experimental data; nor is there adequate evidence for the Herzfeld-Klinger (66) theory that thrombin removes some hypothetical stabilizers of fibrinogen. Many workers have accepted the original thesis of Schmidt (134) (135), that thrombin is a proteolytic enzyme which acts on fibrinogen to form an insoluble split product, fibrin. The supporting experimental evidence is as follows:

a. One of the distinguishing features of enzyme reactions is that the enzyme itself may not be significantly destroyed during the reaction which it accelerates. With the aid of a quantitative method of measuring free thrombin, (94a) (140) it has been found that when thrombin and fibrinogen are mixed, there is no decrease in the free thrombin concentration until the very moment of coagulation, when a large proportion suddenly disappears from the fluid, presumably having been taken up into the clot (24). Klinke (84) observed the process of coagulation nephelometrically, and obtained a similar type of curve upon plotting the degree of turbidity against time, which suggests that the disappearance of thrombin parallels the appearance of visible fibrils. The fact that thrombin does not disappear until the very moment of coagulation strongly suggests that it is merely carried down with the clot, perhaps adsorbed onto its fibrils, as suggested by Foà (34a), Gessard (51a), and Mellanby (94a). The adsorption theory is further supported by the finding that the amount of thrombin which disappears during coagulation varies with the amount used, and with a sufficient excess of thrombin, may actually exceed several hundredfold the minimal quantity necessary for coagulation. The disappearance of thrombin during the coagulation reaction therefore probably does not reflect chemical combination with fibrinogen, but seems rather to be due to its adsorption by the needles of the fibrin clot. This is further supported by the finding (Gamgee, Howell (70)) that free thrombin can be recovered from the dried fibrin.

b. Tsunoo (147) has clearly demonstrated that the kinetics of the fibrinogen-thrombin reaction follow no simple equation such as that of a bimolecular reaction, and offer no clue to the nature of the reaction. As he and others (24) (39a) (140) have pointed out, none of the various "formulas" which attempt to correlate the coagulation time with some exponential of the thrombin or fibrinogen concentration holds throughout the entire range of concentrations, and none offers any clue to the nature of the reaction.

The available data with respect to the temperature coefficient (86) (93) are inconclusive, but consistent with the enzyme theory. Similarly, the optimum pH for the interaction between thrombin and fibrinogen is approximately pH 6.4 to 6.6 (26) (86) (39a), a finding compatible with the thesis that thrombin is a proteolytic enzyme. It is significant that this optimum pH coincides with that for the coagulation of fibrinogen by proteolytic snake venoms (26).

c. A given thrombin thrombin preparation may, under favorable conditions, coagulate at least 2000 times its own weight of fibrin. For example, 10 cc. of horse thrombin solution containing 0.21 per cent protein, clotted 3000 cc. of a solution of horse fibrinogen containing 1.52 per cent fibrinogen. The supernatant fluid expressed from the clot contained 0.15 per cent protein. Even if we correct for the possibility that all the thrombin protein is adsorbed in the clot, this implies that 21 mgm. of a thrombin preparation had formed 41 grams of fibrin. Dog thrombin is even more active. Since the active principle in these crude thrombin preparations probably represents only a minute proportion of the total protein, it follows that thrombin as such can transform many thousand times its own weight of fibrinogen to fibrin. Such a disparity strongly suggests an enzyme reaction (cf. 24, 103a).

d. It has recently been found in this laboratory that papain, a proteolytic enzyme derived from the plant papaw, actively coagulates fibrinogen to form soft clots resembling those formed by thrombin (28). Unlike trypsin, which transforms prothrombin to thrombin, but has no direct coagulating action on fibrinogen, papain does not convert prothrombin to thrombin, but coagulates fibrinogen directly.[6] The latter reaction takes place over a limited range of concentrations, as the enzyme in excess rapidly digests the formed clot, and in sufficient excess hydrolyzes the fibrinogen to non-coagulable split products without passing through the intermediate gel stage.

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[6] Cf. note 5, page 108.

e. It has also been found (26) that the coagulative action of numerous snake venoms (Crotalus adamanteus, Crotalus terrificus, Crotalus horridus, Bothrops nummifera, and others) probably rests on the fact that they contain proteolytic enzymes which act on the fibrinogen, independent of the presence of calcium, platelets or prothrombin. These venoms are effective in high dilution, and their ability to coagulate fibrinogen varies directly with their proteolytic activity as tested with gelatin. Moreover, the pH optimum for their coagulative action on fibrinogen coincides with the pH optimum for the action of thrombin.[6]

Despite the fact that most workers in the field have discarded the enzyme theory as to the nature of thrombin, the foregoing data indicate that it is still the most satisfactory explanation for the transformation of fibrinogen to fibrin. Perhaps no one of the points summarized in the preceding paragraphs is itself conclusive: yet, in the aggregate, they constitute a formidable array of experimental evidence for the enzyme theory. Moreover, some of the data which have been adduced against this theory would seem to be in error. Thus, it has been claimed as evidence for the stoichiometric combination of thrombin with fibrinogen, as opposed to the enzyme theory, that there is under certain conditions a linear relationship between the amount of thrombin used and the amount of fibrin formed (70) (127) (140). However, the determination of the quantitative relationships is an inexact and misleading experiment (24). With a large excess of thrombin the fibrinogen is coagulated almost quantitatively, within a few hours, and the amount of fibrin formed depends solely upon the amount of fibrinogen used. As less and less thrombin is used, coagulation becomes slower and slower, and equilibrium becomes increasingly difficult to define. If the clot is expressed after 24 hours in the icebox, the supernatant fluid often clots afresh, and fibrin may be formed continuously for as long as 72 hours. By this time more than 75 per cent of the thrombin has deteriorated spontaneously or has been adsorbed by the clot, invalidating the equilibrium results obtained. With very small amounts of thrombin, coagulation is so slow, and the clots formed so tenuous, that the results are devoid of quantitative significance. The quantitative relationships between thrombin, fibrinogen and fibrin would therefore seem to offer no reliable clue to the nature of the reaction.

Again, the fact that thrombin disappears during the coagulation reaction hardly suffices to disprove the enzyme theory. Enzymes are frequently inactivated during the reactions which they catalyze; and it is further probable that thrombin is non-specifically adsorbed by the formed fibrin (cf. page 109). It is true that no direct evidence has ever been given for a proteolytic action of thrombin on fibrinogen, except for a brief unconfirmed report by Fuchs and Zakrzewski (49); but such proteolysis is extraordinarily difficult to demonstrate in solutions containing only 1/200,000 mole of the active substance per liter, and which gel under the influence of the hypothetical proteolytic agent.

The claim by Hammarsten (57) (58) and by Mellanby (93) that thrombin splits fibrinogen to form fibrin and a water-soluble globulin is difficult to reconcile with the observation in this laboratory that fully 95 per cent of the protein in solutions of fibrinogen may be recovered in the clot, unless one makes the *ad hoc* assumption that the hypothetical globulin is only 1/20 as large as the fibrinogen molecule.

There is no significant change in pH during the coagulation of fibrinogen by thrombin (cf. page 100). The absence of such change in unbuffered solutions of protein renders highly suspect reported changes of as much as 0.3 pH in such strongly buffered systems as whole blood or plasma. Changes of this magnitude reflect the release of comparatively large quantities of acid or base, and are probably to be ascribed either to experimental error, or uncontrolled factors such as the loss of CO_2. The finding of a constant hydrogen ion concentration during the coagulation reaction is wholly consistent with the theory that thrombin is a proteolytic enzyme, as witness the approximately constant pH during tryptic digestion: each peptide linkage would on hydrolysis form one amino and one carboxyl group, with little or no *net* change in pH of the solution.

The bulk of evidence just cited indicates that thrombin is a proteolytic enzyme. Similarly, the observation that prothrombin is converted to thrombin by crystalline trypsin and certain proteolytic snake venoms, suggests that calcium and platelets may together constitute a similar proteolytic enzyme which reacts with prothrombin to form thrombin. It thus becomes a plausible working hypothesis, wholly consistent with the known facts, that physiological coagulation is a comparatively simple reaction which involves two consecutive enzyme reactions (cf. table II). As seen in the table, this possibility finds a complete analogy in the recently discovered (85) activation of chymotrypsinogen by trypsin to form chymotrypsin.

III. THE NATURE OF THE PHYSIOLOGICAL ANTICOAGULANT

Circulating blood apparently contains all the reagents necessary for the formation of thrombin (prothrombin, platelets, calcium).

TABLE II

A Working Hypothesis as to the Mechanism of Blood Coagulation

SUBSTRATE		ACTIVATING ENZYME		ENZYME PRODUCT
1. Prothrombin	+	Calcium + platelets Trypsin Certain proteolytic snake venoms* Bacterial proteases?	→	Thrombin, a proteolytic enzyme which converts fibrinogen to fibrin, and which can be replaced by other enzymes (papain, numerous proteolytic snake venoms,† and perhaps by bacterial proteases).
A complete analogy to this hypothesis is furnished by the recently described activation of chymotrypsinogen by trypsin (85)				
2. Chymotrypsinogen	+	Trypsin	→	Chymotrypsin

* Notechis scutatus (Australian tiger snake); Bothrops atrox (fer-de-lance); Bothrops jararaca (jararaca); Crotalus terrificus basiliscus (Mexican cascabel); Mixed micrurus venom (mixed coral snakes).

† Crotalus adamanteus (Florida diamond back); Crotalus horridus (timber rattler); Crotalus terrificus terrificus (Brazilian cascabel); Bothrops atrox (fer-de-lance); Bothrops jararaca (jararaca); Bothrops nummifera (Mano de Piedra).

The failure of circulating blood to clot *in vivo* is one of the most puzzling aspects of the general problem. Numerous theories have been suggested, and the several anti-, pro-, antipro-, and proanti- factors which these theories invoke represent ingenious but mutually exclusive *hypotheses* as to the nature of the body's defense mechanism against intravascular coagulation. We may preface the following discussion by the opinion that no satisfactory explanation, adequately supported by experimental data, has yet been offered for the failure of circulating blood to clot.

A. Pro-Prothrombin (Proserozyme)

Bordet (11) suggested that circulating blood contains, not prothrombin ("serozyme") as such, but an inactive precursor of prothrombin which he termed proserozyme. This precursor is presumably converted to prothrombin only when it comes in contact with some foreign surface, such as glass. The supporting experimental evidence is meager. Moreover, the fact that thrombin production and coagulation can be initiated *in vivo* by the injection of either tissue extracts, trypsin (28), or snake venoms (26) indicates that, contrary to the thesis of Bordet, circulating prothrombin can be activated to thrombin directly.[7]

B. Antithrombin

A second factor which has been suggested as contributing to the non-clotting of blood is the presence in circulating plasma of an antithrombin. It is well known that the thrombic activity of fresh serum rapidly decreases; and if inactive serum is added to some fresh thrombin, and the mixture allowed to stand for 30 minutes, the coagulating activity of the latter may no longer be demonstrable. Although the reaction has been extensively studied, the nature of the antithrombic factor in serum is still unknown. Citrated or oxalated plasma contains this same factor, and there is every reason to believe that it is present in circulating blood.

The possible physiological value of a circulating antithrombin in counteracting small quantities of thrombin which might be liberated *in vivo* is obvious. Indeed, even in the test tube coagulation occurs only by virtue of the sudden liberation of a large excess of thrombin. If the same amount of thrombin were liberated slowly, it would be inactivated by the antithrombin before it could react with fibrinogen, and coagulation would be either delayed or entirely prevented. The occasional failure of platelet-free citrated horse plasma to clot upon the addition of calcium is probably chiefly due to this factor.

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[7] Unless one assumes that these agents not only convert prothrombin to thrombin, but also convert pro-prothrombin to prothrombin. Similarly, in the case of the several inhibitor theories (Howell, Fuchs, Mellanby-Pickering; cf. page 000) one must make the unlikely assumption that the agents which convert prothrombin to thrombin *in vivo* are also able to split it from the hypothetical inactive complex.

Granted the value of a circulating antithrombin in counteracting the slow liberation of small quantities of thrombin, it is nevertheless clear that it can be of only secondary importance in preventing coagulation. Contrary to early reports (19) (70) (155), coagulation has been produced *in vivo* by Mellanby (96), Mills and Matthews (105), and in this laboratory, by the intravenous injection of comparatively small quantities of an active thrombin. The very fact that shed blood does clot can only mean that its antithrombic activity is not sufficient to counteract the explosive liberation of thrombin such as occurs in the test tube.

Protocol 1. The production of coagulation in rabbits in vivo by the intravenous injection of thrombin

Rabbit and horse thrombin were prepared from Berkefeld-filtered plasma by the Mellanby technic, and 30 to 40 cc. were injected intravenously into rabbits weighing 2.5 to 3.0 kilos, 2 minutes being taken for the injection. Five of the twelve animals injected[8] died in convulsions in three to ten minutes after beginning the injection. On immediate autopsy, large soft clots were lying free in the major vessels (inferior vena cava, auricles, and in two cases, the aorta); and the fluid blood surrounding these soft clots was found to be fibrinogen-free (no precipitate on 50 per cent saturation with NaCl or after heating at 56°C.; not coagulable by thrombin). In two of the seven animals which survived, the blood was found to be almost fibrinogen-free ten minutes after the injection. This indicates that coagulation had occurred, but so slowly that the body had been able to dispose of the clots before they blocked a vital vessel.

The quantity of the thrombin solution found effective (30 cc., or 12 mgm. protein) represented approximately one part of thrombin solution to seven parts of circulating blood. As is indicated in the following table, this approximated the amount necessary to clot citrated blood from the same animal in the same time interval (three to ten minutes) *in vitro*.

Citrated plasma, cc.	1	1	1	1	1	1	1
Thrombin, cc.	0.8	0.4	0.2	0.1	0.05	0.025	0.0125
Coagulation time, mins.	1½	3	8	20 Incomplete, soft clot	No clot formed in one hour		

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[8] Three out of six injected with horse thrombin; two out of six injected with rabbit thrombin.

C. Prothrombin Inhibitors

Since the circulating blood contains prothrombin, and since this prothrombin is converted to thrombin only *after* the blood has been removed from the body, it would appear that the chief protective mechanism of the body against intravascular coagulation is one which prevents this transformation of prothrombin to thrombin *in vivo*. This, perhaps the most important single aspect of the coagulation phenomenon, is still one of its greatest puzzles. Four distinct explanations have been given for the fact that prothrombin is converted to thrombin only after blood has been shed, and none of the four is wholly satisfactory.

1. The suggestion of Bordet (9, 10, 11) that circulating blood contains an inactive precursor of prothrombin, which is activated to prothrombin only on contact with a foreign surface, is not supported by adequate experimental data (cf. page 114).

2. Similarly, there is no satisfactory evidence that the prothrombin of circulating blood is in combination with fibrinogen or other plasma proteins, and is liberated only when the blood comes in contact with some foreign surface (Feissly (35); Mellanby (93); Pickering (121, 122)). This theory is contradicted by the ease with which prothrombin may be separated from fibrinogen in the test tube (cf. page 101), and second, by the fact that coagulation can be readily induced *in vivo* by agents which affect either prothrombin[9] (tissue extracts, trypsin, snake venom) or fibrinogen (thrombin, papain, snake venoms).

3. *Heparin.* Howell and Holt (80) extracted a substance from liver which inhibited blood coagulation, and which was termed heparin. In later studies (76), methods of purifying this substance were described, and preparations were obtained which were so active that one part inhibited the coagulation of 100,000 parts of blood for 24 hours. This heparin was believed to prevent coagulation by combining with prothrombin, binding the latter so that it could no longer react with calcium and platelets to form thrombin. It was therefore termed antiprothrombin. Because the antithrombic action of plasma was increased by the addition of heparin, it was suggested that plasma contains a "pro-antithrombin" which reacts with heparin to form an

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[9] Cf. note 5, page 108.

active thrombin inhibitor. The anticoagulant action of heparin was accordingly considered to be twofold: (a) combination with the plasma prothrombin; and (b) the formation of antithrombin from an inactive plasma precursor.

Because of the large quantities found in the liver, and the subsequent demonstration of a similar substance in serum (43, 76) heparin was believed to be of physiological importance in preventing intravascular coagulation. In the Howell scheme, when blood is shed, the platelets disintegrate and release a substance which may be related to cephalin. This platelet factor combines with the antiprothrombin (heparin) and thereby releases the free prothrombin, which then reacts with calcium to form thrombin. Platelets accordingly would not react with prothrombin directly, but would serve merely to release it from an antiprothrombin, identified with the substance extracted from liver, heparin.

The demonstration of a heparin-like substance in serum is certainly cogent evidence that it is part of the physiological defense mechanism against intravascular coagulation. The fact that the quantity so demonstrated falls far short of that required might be reasonably ascribed to losses during the process of purification. However, as is indicated in the following experiments, there is reason to doubt that heparin is an antiprothrombin, or that the function of the platelet factor is to *combine* with the heparin and thus release prothrombin. Indeed, it is debatable whether heparin is of physiologic significance in preventing intravascular coagulation.

(a) Incubation of a mixture of platelets and a prothrombin solution does not affect the rate of thrombin production upon the subsequent addition of calcium (23). If platelets acted by releasing prothrombin from combination with an anti-factor, this preliminary incubation might reasonably be expected to accelerate the rate of thrombin production by providing the free prothrombin, ready for activation.[10]

(b) If platelets, tissue extracts, or cephalin serve merely to combine with heparin present in blood as a heparin-prothrombin compound, they should promote coagulation only so long as they continue to liberate prothrombin from its hypothetical union with heparin. Moreover, within that limit, the amount of thrombin formed should increase directly with the amount of platelets or cephalin used. Instead, if serially increasing amounts of platelets or cephalin are added to a platelet-free plasma (or prothrombin solution) one finds that a minimal amount of platelet or tissue derivative suffices for the maximal production of thrombin, and even a thousand-fold excess does not further increase the *amount* of thrombin formed. The cell derivative does, however, cause a progressive and striking increase in the *rate* of thrombin production, and thus, in the velocity of coagulation (23). It follows that the platelet or tissue factor accelerates the transformation of prothrombin, but apparently does not act by combining with heparin and thus liberating prothrombin from a hypothetical heparin-prothrombin compound.

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[10] Unless one makes the *ad hoc* assumption that the hypothetical preliminary reaction involving the release of prothrombin is very rapid as compared with the reaction between prothrombin and calcium.

(c) Clowes (16) has found that if cephalin is added to citrated plasma, and if the cephalin-plasma mixture is then passed through a Berkefeld filter, the lipoid is retained by the filter, and the plasma filtrate does not coagulate promptly on the addition of $CaCl_2$, unless more cephalin is added. The experiment of Clowes has been repeated and confirmed in this laboratory, using both platelets and aqueous tissue extracts instead of cephalin. In other words, cephalin, platelets and tissue extracts do not activate prothrombin in the absence of calcium; yet on the Howell theory, they should have released the prothrombin from its combination with the hypothetical "anti-prothrombin," and the Berkefeld filtrate should have contained free, reactive prothrombin.

(d) As reported by Mellanby (97) and Quick (124), and confirmed in this laboratory, heparin not only prevents the formation of thrombin from prothrombin, but also acts as an antithrombin. Its addition to plasma or fibrinogen necessitates the addition of larger quantities of thrombin to effect coagulation than would otherwise be necessary. It thus seems to counteract both phases of coagulation, and is not specifically an antiprothrombin. It is possible that this antithrombic action is due to an associated impurity rather than the heparin per se. It is nevertheless clear that the antithrombic action of most heparin preparations enjoins caution in ascribing a "pro-antithrombic" function to heparin (cf. page 117).

(e) Charles and Scott (15) have prepared a heparin-like substance from beef lung; indeed, the yield was greater than in the case of liver. Fuchs (43) has also prepared an anticoagulant from many tissues other than liver. These two observations suggest that heparin itself may be an artificial product of tissue manipulation, rather than a specific functional secretion of the liver.

In summary, heparin apparently prevents coagulation both by retarding the formation of thrombin and by acting as an antithrombin. The experimental data cited in the foregoing paragraphs do not support the theory of Howell that heparin combines with prothrombin, or that platelets release free prothrombin from this inactive compound by combining with heparin. Moreover, there is reason to doubt that heparin is a physiological secretion of the liver which prevents blood coagulation *in vivo*. The quantities prepared from blood are only a minute fraction of the amount necessary to prevent coagulation *in vitro*; and a similar anti-coagulant has been prepared from tissues other than the liver.

D. Platelet Stability

The factor which is generally considered to be the most important in preventing blood coagulation *in vivo* is the stability of the blood platelets in the circulating blood. The essential rôle of the platelets in reacting with prothrombin and calcium *in vitro* to form thrombin has already been discussed. Presumably, it is only after blood has been shed that the platelets disintegrate and release the substance primarily concerned in this reaction. According to Cramer and Pringle (18), Clowes (16) and Ferguson (37) calcium is essential for this disintegration; and numerous investigators (37, 143, 157) have actually seen platelets clump and disintegrate on the addition of calcium. Aynaud, and Lampert (87) have stressed the fact that contact with a foreign surface onto which the platelets can be adsorbed is essential for this dissolution.

Granted that platelets may disintegrate under certain conditions, it has never been definitely proved that such complete dissolution is a necessary preliminary to coagulation. Instead, the following experiment suggests that platelets, or platelet fragments sufficiently large to be centrifuged, may yet be capable of initiating thrombin production. If, beginning with citrated plasma, one prepares a thick suspension of washed platelets resuspended in 0.85 NaCl or Ringer's solution, and then adds calcium in physiological concentration, and if the suspension is then centrifuged at high speed after ½ to 1 hour incubation, with or without the addition of serum, the original coagulating activity of the platelet suspension is recovered almost quantitatively in the sediment. This indicates that formed platelets, or fragments so large as to be readily centrifuged, are capable of accelerating coagulation. Moreover, if such a suspension of washed platelets is injected intravenously, there is prompt intravascular coagulation and death, with large soft clots in the heart and large vessels.

If something must happen to platelets in shed blood before they can initiate coagulation, these observations suggest that it may not necessarily be the complete disintegration described by Tait and Burke (143), Wright and Minot (157) and others (cf. Ferguson, 37).

However, whether the platelets must disintegrate completely, or whether there is some more subtle transformation, is of secondary importance as compared with the question: what happens in shed blood which activates the platelets and thus enables them to transform prothrombin to thrombin? It has been suggested that they are "activated" by contact with a foreign surface such as glass. The nature of this "activation" is, however, wholly obscure; and it is conceivable that some as yet wholly unsuspected mechanism is involved. The inhibiting effect of cysteine in blood coagulation, noted by Mueller and Sturgis (112), and the possible rôle of a negatively charged glass surface as an adsorbent for positively charged particles in the blood (52), are suggestive in this connection.

It is obvious that the nature of the physiological anticoagulant, that is, the mechanism whereby the blood is kept from coagulating *in vivo*, is still one of the unsolved aspects of the coagulation problem. It is clear also that its eventual solution will throw considerable light on the sequence of events which precede thrombin formation *in vitro*. The simplest working hypothesis is that platelets are somehow activated in shed blood to release the active principle; and this active principle may well be a proteolytic enzyme resembling trypsin (cf. pages 108, 113).

IV. COAGULATION IN VARIOUS PATHOLOGICAL CONDITIONS

In keeping with our present imperfect understanding of the process of normal coagulation, but little progress has been made in studying the serious disturbances in the coagulability of blood which occur in hemophilia, jaundice, purpura hemorrhagica and, in experimental animals, as a result of anaphylactic shock. Similarly, although there is some evidence that thrombosis, red cell sedimentation, and the deposition of fibrin at sites of inflammation are all closely related to physiological coagulation, the mechanism of these three phenomena and their exact relationship to the coagulation reaction require further study.

A. The Coagulation Deficiency in Hemophilia

The characteristically prolonged coagulation time noted in hemophilic patients is presumably the cause of their tendency to bleed for long periods of time after relatively slight injuries. The reason for this delayed coagulation is as yet unexplained. Almost every factor concerned in blood coagulation has been held by various workers to be at fault; yet the more recent studies indicate that every known factor is present in normal concentration.

1. Thus, the decreased prothrombin content reported in early studies (83, 40, 74) is denied by numerous investigators (1, 25, 34, 79, 125, 152) and is clearly in error.

2. The presence of increased amounts of antithrombin (150a, 43) has not been confirmed (1, 25, 79, 111, 125); the latter investigators have clearly shown that hemophilic blood is as readily clotted by thrombin as normal blood. The presence of a prothrombin inhibitor (34) (43) is rendered improbable by the fact that the addition of hemophilic blood does not retard the coagulation of normal blood (1) (31) (119b) (150a).

3. Much of the controversy as to the coagulative deficiency in hemophilia has centered around the platelets. (a) Thus, it has been suggested that hemophilic platelets are less active than normal platelets (36, 40, 106), and that this difference in reactivity is more pronounced in hemophilic blood than it is in normal blood (36) (119a). Wöhlisch (152), however, found that in one of three hemophilics the

platelets seemed functionally normal. In this laboratory we have been unable to find any difference in the reactivity of normal and hemophilic platelets (25), a finding recently confirmed by Patek and Stetson (119b). (b) It may be that the blood platelets are more stable in hemophilia than normally (79, 106, 119a); but this reported stability does not seem to affect their coagulating function. (c) Although it is unquestionably true that the addition of tissue extracts or excess platelets makes hemophilic blood coagulate within normal limits (25, 98, 111, 132) this fact hardly proves that the platelets are at fault, for even normal blood coagulates faster on such addition.

4. An entirely different explanation of the coagulative deficiency in hemophilia was given by Addis (1), who found that the blood prothrombin in such cases, although of normal concentration, was *qualitatively* altered insofar as it was only slowly activated to thrombin; and this slow activation explained the delayed coagulation. Addis' findings have been recently confirmed in this laboratory (25) by measuring the rate and degree of thrombin production in solutions of prothrombin prepared in similar manner from normal and from hemophilic blood. The rate of thrombin formation was uniformly slower in the latter. *Either normal or hemophilic platelets* added in sufficient quantity accelerated thrombin formation to the normal level.

Given this delayed formation of thrombin as the probable cause of the retarded coagulation in hemophilia, and given the observation that the washed platelets seem functionally normal, the reason for the retarded activation of prothrombin remains wholly obscure. That there is actually a qualitative change in hemophilic prothrombin is supported by the finding of Mills (98), which we have been able to confirm, that cephalin, unlike platelets, has relatively little effect on hemophilic blood, although it markedly accelerates the coagulation of normal blood. On the other hand, recent unpublished experiments by Eagle and Tocantins indicate that hemophilic blood coagulates normally on the addition of snake venoms which convert prothrombin to thrombin, a finding which does not support the theory of a qualitative prothrombin deficiency. The cause of the retarded coagulation in this disease is clearly an open question, with every explanation yet suggested rendered improbable by convincing experimental data.

The treatment of hemophilia has been largely empirical. Blood transfusions are of temporary value in decreasing the hemorrhagic tendency, and probably hasten coagulation by supplying normal prothrombin. Snake venoms have recently been used to arrest bleeding from the skin and mucous membranes. Peck (120) has reported clinical improvement on the intradermal injection of moccasin snake venom (0.2 cc. of a 1:3,000 solution) once or twice weekly. In the test tube, this venom acts as an anticoagulant, as it destroys both fibrinogen and prothrombin (26). Its clinical effect has been tentatively ascribed by Peck to an action on the blood vessels. Rosenfeld and Lenke (128) have used the actively coagulating venom of the Australian tiger snake (Notechis scutatus) as a local styptic in cases of external bleeding; MacFarlane and Barnett (90a) have similarly used the venom of Vipera russellii. The venom in 1:5,000 or 1:10,000 dilution is applied as a wet compress.

The report that hemophilic individuals do not excrete ovarian hormone, as do normal men, and that the administration of the hormone is followed by a decreased bleeding time and decreased tendency to hemorrhage (8) has not been confirmed (81, 139).

Eley, Green and MacKhann (30) have revived the peroral administration of tissue extracts as a means of lowering the coagulation time, and have used extracts of human placenta for this purpose (113) (152, pp. 329, 476, 599). To what extent such extracts are absorbed unchanged, and to what extent the coagulation is accelerated, are subjects of continued study.

B. The Coagulation Deficiency in Thrombocytopenic Purpura

Despite the characteristically low platelet count, the coagulation time of the blood in cases of purpura hemorrhagica is usually within normal limits. This contradiction is explained by the observation that the amount of platelets normally present in the blood (200,000 to 500,000 per cubic millimeter), represents a large excess. Even a small fraction of this concentration usually suffices to induce coagulation of platelet-free plasma within approximately normal time (119).

No satisfactory explanation has yet been offered for the fact that subcutaneous and joint hemorrhages are observed in purpura hemorrhagica despite the presence of sufficient platelets to cause coagulation *in vitro* within normal time limits. Although purpura has been produced experimentally by the injection of antiplatelet serum in rabbits (6, 88, 129, 130, 146), there is considerable doubt that the thrombocytopenia per se is the causative factor. The therapeutic effect of splenectomy in purpura does not depend on an increased platelet count, as it may persist after the count has fallen to its pre-operative level. Both Roskam (129, 130) and Mackay (91) point out that purpura may be observed in the absence of thrombocytopenia, and conversely, that there may be a pronounced fall in the platelet count without an associated tendency to subcutaneous hemorrhage, and without an increased bleeding time. Bedson (6) stresses an increase in the capillary permeability as an essential part of the disease syndrome. Mackay suggests that the inability of the vessels to contract is of primary importance in causing hemorrhage, rather than the thrombocytopenia. Roskam also suggests that the blood vessels must be considered as contributing to the disease syndrome, a possibility considered by both Aschoff and Krogh.

The well-known clinical observation that patients with purpura hemorrhagica have a prolonged bleeding time (21, 22) after a minute sharp stab wound in the subcutaneous tissue, despite the fact that the blood clots within normal time limits *in vitro*, is as yet unexplained. It may be related to some obscure change in the capillary endothelium, as just discussed. It may also be caused by the fact that the clot in this condition does not retract to squeeze out serum and thus assume a certain firmness, as it does normally, but remains a soft non-retractile gel, of little value as a mechanical plug. Finally, it seems probable that the intravascular platelet-thrombi which normally form within the cut vessels are deficient or absent in this condition.

The mechanism of clot retraction is as yet unknown, other than the fact that large numbers of platelets are essential. A detailed discussion is given by Lampert (87), who maintains that platelets adsorbed onto a foreign surface act as foci where coagulation proceeds more rapidly than in the body of the solution. Fuchs (45) finds that the size of the fibrin needles varies according to the speed of their deposition. Presumably, coagulation begins in the immediate vicinity of each platelet; he suggests that the resultant uneven distribution of fibrin sets up strains in the fibrillar gel which result in its contraction. Tocantins (146) has recently proposed an alternative explanation based on the observation that after the fibrils have formed, platelets converge to form agglutinated masses at fibril-intersections. This presumably results in the twisting and shortening of the fibers. Finally, the so-called retraction of the clot has been ascribed by Hirose (67) to its actual digestion. Mills and Ling (103a) have made a similar suggestion. Further study is clearly indicated.

C. Blood Coagulation Following Anaphylactic Shock

It is well established that after anaphylactic shock, the blood coagulates either slowly or not at all (Arthus (1a); Biedl and Kraus (7a); Modrakowski (107); and numerous others). Fibrinogen (90), prothrombin (161), and platelets (88a) (136a) have all been reported to be deficient after anaphylactic shock, while other investigators find these factors to be normal. Zunz and La Barre (161) have also reported an increased amount of antithrombin. Eagle, Johnston and Ravdin (29) have recently found that anaphylactic shock in dogs and rabbits does not affect the fibrinogen, prothrombin, platelets, or calcium, but does cause an extraordinary increase in the antithrombin content of the plasma, in some cases amounting to a hundred-fold increase above the original level. The prolongation of coagulation time in individual animals was paralleled by the increased antithrombin content of the plasma; and in guinea pigs, in which shock did not affect the coagulation time, there was no demonstrable change in the plasma antithrombin. They concluded, in confirmation of Zunz and La Barre, that the prolonged coagulation time caused by anaphylactic shock may be ascribed to the sudden release of large quantities of antithrombin.

The origin of antithrombin and the mechanism of its action are as yet unknown. It may be noted that it inactivates, not only the thrombin formed from prothrombin by calcium and platelets, but also that formed from prothrombin by trypsin or certain snake venoms. This is further evidence that the thrombin formed by these three agents is identical (cf. page 108). On the other hand, antithrombin has no demonstrable effect on those enzymes other than thrombin which act directly on fibrinogen and convert it to a fibrous gel apparently identical with fibrin (cf. pages 110–111). The coagulating activity of papain, or of Crotalus venoms, is unaffected by antithrombin.

D. *The Coagulation Deficiency in Jaundice*

It is common experience (cf. Carr and Foote (12)) that patients with jaundice tend to bleed after surgical operations. Numerous explanations have been offered for the observation. The problem is complicated by the fact that the coagulative deficiency is not due to the jaundice as such, for most patients with jaundice have normal coagulation times, and undergo surgical treatment with no difficulty. Dogs with intense obstructive jaundice generally have a normal coagulation time. It has been reported (125) that the bleeding occasionally observed in jaundice is due to a prothrombin deficiency; while Bärlik (4) finds increased quantities of an antiprothrombin.

E. *The Mechanism of Thrombosis*

Fresh thrombi consist essentially of a laminated deposit of fibrin which contains large numbers of platelets and may contain relatively few red and white blood cells. An ingenious and simple experiment reported by Harrison and Mason (60) suggests that such thrombi are merely the result of a localized intravascular coagulation, and that red blood cells are often relatively few because they are swept away by the circulating blood before they can be enmeshed. In the experiment, heparinized blood was passed along a glass tube into which protruded a wick carrying a solution of tissue extract. After a suitable interval, a laminated deposit of fibrin was found to have formed around the end of the wick which resembled thrombi *except for the absence of platelets.* The authors suggest that tissue juices liberated at foci of infection or injury along the vessel wall cause the localized formation of thrombin and coagulation. This theory fails to explain the facts that true thrombi, unlike these produced experimentally, contain large numbers of platelets, and that the formed thrombus may grow by the accretion of platelets until it extends far beyond the injured area. Moreover, one would expect the circulating blood to wash away the tissue juices as fast as they were released at an injured area of the vessel wall. It seems a better working hypothesis to assume that platelets accumulate at the focus of injury in adherent agglutinated masses; and that fibrin is subsequently deposited within and around this clump of platelets by virtue of the fact that the "altered" platelets initiate a localized formation of thrombin. Ferguson (37b) has presented evidence in this direction.

F. Fibrinogen and the Sedimentation Rate of Red Blood Cells

It has been known since ancient times that the red blood cells tend to settle out faster in certain pathological conditions. It has been definitely established that this more rapid sedimentation is due to the exaggerated formation of rouleaux, the spontaneous agglomeration of the disc-like red cells into neatly-stacked cylinders (32, 59).

Numerous theories have been suggested for the mechanism of this rouleaux formation. That most generally accepted is that it is due to an increased amount of fibrinogen in the plasma. Nevertheless, recent studies in this laboratory indicate that fibrinogen and rouleaux formation (or sedimentation) are not causally related. The pertinent experimental data may be briefly summarized as follows:

1. Although individuals with a rapid sedimentation time usually have an increased fibrinogen content, this is not invariable. Even a high degree of correlation would not suffice to prove that it is the fibrinogen per se which is causing the increased sedimentation.

2. Complete removal of fibrinogen, whether by heating the plasma at 56°C. for 5 minutes, by coagulating citrated plasma with $CaCl_2$, by coagulating plasma or whole blood with trypsin, by defibrinating whole blood, or by salting out the fibrinogen with either NaCl or $(NH_4)_2SO_4$, results only in a 10 to 40 per cent decrease in the sedimenting activity of the plasma.[11] Clearly, the reactive factor is not fibrinogen as such, but something only in part associated with the fibrinogen fraction of the plasma proteins.

3. Fibrinogen purified by several precipitations with either NaCl or $(NH_4)_2SO_4$ and redissolved in concentrations comparable to those which are found in actively sedimenting plasmas, is relatively inactive in causing sedimentation.

The conclusion seems warranted that fibrinogen *per se* is not the cause of rouleaux formation and the resultant sedimentation of red blood cells.

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[11] The amount of sedimentation after a given interval is not a direct measure of the sedimenting activity of the particular plasma. Considerable confusion has been caused by the erroneous assumption that there is a *linear* correlation between the rate of sedimentation and the plasma concentration of the substance responsible for that sedimentation.

G. The Deposition of Fibrin at Foci of Inflammation

The regular presence of fibrin in the intercellular fluid at sites of inflammation, and the possible rôle of this fibrinous network in walling off the affected area and preventing the spread of the toxic agent, require no discussion. Despite the importance of the phenomenon, but little work has been done towards ascertaining the precise mechanism whereby fibrin is thus deposited in the tissue spaces. Recent work indicates several promising lines of attack.

Thus, incident to the inflammatory response, there may be a local accumulation of tissue extractives which function like platelets, and initiate thrombin production. Again, since proteolytic enzymes like trypsin and papain have been shown to cause coagulation, (the former by converting prothrombin to thrombin, the latter by a direct action on the fibrinogen), and since both polymorphonuclear leucocytes and mononuclear wandering cells are known to contain or to elaborate proteolytic enzymes (150b, page 79), the deposition of fibrin at foci of inflammation may well be incidental to the cellular response, and due simply to enzymes released by the cells. Finally, it is a well known observation (54, 56, 149) that many bacteria such as Staphylococci, Bact. coli, Proteus vulgaris, B. subtilis and numerous others, will, if introduced into plasma, cause its coagulation. Accordingly, the large amounts of fibrin found at areas of bacterial infection may in some cases be due to metabolic products of the bacteria themselves.

Tillett, Garner and Edwards (144, 144a) have found in filtrates from certain streptococcal cultures a lysin which causes the dissolution of fibrin clots. The appearance of anti-fibrinolysin in the blood of patients recovering from streptococcal infections is an interesting and provocative finding. The nature of this streptococcal fibrinolysin, and the relation of the lysis it causes to that which sometimes occurs spontaneously in sterile plasma or fibrinogen clots, are as yet unknown.

SUMMARY

The available evidence indicates with a strong degree of probability that the phenomenon of blood coagulation involves two consecutive reactions: the first is the interaction between prothrombin, calcium and platelets (or tissue extracts) to form thrombin; the second involves the reaction of thrombin with fibrinogen to form fibrin. The kinetics of the calcium-platelet-prothrombin reaction, and the recent finding that trypsin or certain proteolytic snake venoms can replace calcium and platelets, and alone activate prothrombin to thrombin, strongly suggest that calcium and platelets together constitute a proteolytic enzyme analogous to trypsin which reacts with prothrombin to form thrombin.

With respect to the reaction between thrombin and fibrinogen to form fibrin, the tendency of the past twenty years has been to veer away from the original concept of Schmidt that thrombin is a proteolytic enzyme which splits fibrinogen to form fibrin. Nevertheless, the data summarized in the text indicate that such is the case. Certainly, it would seem to be the most satisfactory hypothesis yet suggested. The observation that a proteolytic enzyme, papain, and various proteolytic snake venoms also convert fibrinogen to a fibrillar gel resembling fibrin is further evidence in this direction.

The reason for the fact that circulating blood fails to clot is as yet unknown. For reasons cited in the text, the antithrombic action of plasma is an inadequate explanation: and serious objections may be made to the inactive protein-complexes postulated by Pickering and Mellanby, to the proserozyme theory of Bordet, and the heparin theory of Howell. Although the "stability" of the platelets in circulating blood may well be the determining factor, the nature and cause of the change effected in platelets in shed blood is a matter of conjecture only. The fact that suspensions of platelets repeatedly washed in salt solution containing $CaCl_2$ nevertheless retain most of their coagulative activity indicates that the change effected *in vitro* is not necessarily complete disintegration, but some more subtle "activation." Whether this obscure "activation" of the platelets is due to oxidation by atmospheric O_2, loss of CO_2 from the plasma, contact with a foreign surface, or some as yet unknown process, remains to be ascertained.

The available data allow of no definite decision as to the nature of the coagulative deficiency in hemophilia, other than that there is a delayed elaboration of thrombin. The conflicting reports which ascribe this delay to an abnormal platelet stability on the one hand, and to an unidentified qualitative change in the plasma factor on the other, cannot be reconciled, and necessitate further study. No explanation adequately supported by experimental data has yet been offered for the hemorrhagic tendency of patients with thrombocytopenic purpura, despite the fact that there are sufficient circulating platelets to make the blood clot *in vitro* almost within normal limits. Recent work, as yet unconfirmed, suggests that the bleeding tendency occasionally observed in jaundice may be due to a prothrombin deficiency. The non-coagulability of the blood frequently observed in dogs and rabbits after anaphylactic shock may be ascribed with some certainty to a marked increase in the antithrombic activity of the plasma. Finally, there is reason to doubt that there is a causal relationship between the fibrinogen content of plasma and the sedimentation rate of the red blood cells.

The recent production *in vitro* of structures bearing a marked resemblance to thrombi suggests that thrombi are simply *in vivo* blood clots initiated by the agglutination of platelets at foci of irritation along the vessel wall. The mechanism of the intercellular deposition of fibrin at foci of infection and inflammation, and the mechanism of fibrinolysis, must be reinvestigated in the light of the fact that proteolytic enzymes are known to cause the coagulation of blood, as well as the subsequent dissolution of the clot.

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PHRENIC NERVE OPERATIONS IN THE TREATMENT OF PULMONARY TUBERCULOSIS

A Review

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HISTORY

Phrenicotomy or simple cutting of the phrenic nerve was used in the nineteenth century in order to relieve diaphragmatic spasm occurring in tetanus. Sauerbruch paralyzed the diaphragm in animal experiments in order to facilitate operations upon the lower end of the oesophagus. But it was not until 1911 that Stuertz (525) first recommended the production of diaphragmatic paralysis as a therapeutic agent for the treatment of lower lobe bronchiectasis and cavitary processes. Bardenhuer (343), (cited by Matson) in 1912, reported a favorable result upon a case of bronchiectasis, and Oehlecker (399), in 1913, reported three cases of phrenicotomy, one of which was operated upon in 1911. Sauerbruch (478), in 1913, reported phrenic nerve section in five cases, three for tuberculosis and two for bronchiectasis.

Walther (561) showed that there was incomplete paralysis and a return of function in a large percentage of cases upon whom phrenicotomy had been performed. Because of this, the operation was rarely used over a period of almost 10 years. In 1922 Felix (166) and Goetze (204) independently showed that the reason for the inadequacy of simple phrenicotomy was the presence of accessory nerves. In order to produce a permanent paralysis, Felix and Lebsche advocated avulsion of the nerve and Goetze proposed his radical phrenicotomy. Phrenicectomy (phrenic exairesis) became the more popular of the two procedures and immediately was accepted throughout the world as a definite therapeutic measure in the collapse therapy of pulmonary tuberculosis. Thousands upon thousands of diaphragms were paralyzed in the hope of curing pulmonary tuberculosis.

Not only was phrenicectomy used as an independent measure but it was also advocated by Frisch (186) in 1922 as an aid to pneumothorax. Others paralyzed the diaphragm during the course of every artificial pneumothorax.

As the reports of large series of cases from various clinics were published, it became evident that diaphragmatic paralysis was not the "cure all" that it was originally believed to be. Gradually, the indications for phrenic nerve operations have become more and more restricted to a limited group of cases and most phthisiologists consider its greatest usefulness as an adjunct to other collapse procedures. There are on the other hand still some adherents to the use of diaphragmatic paralysis as an adjuvant to bed rest in almost all minimal lesions.

In this review an attempt has been made to present the literature in an unbiased manner. A large series of phrenicectomies has been collected and an attempt made to determine the value of the operation as an independent procedure.

ANATOMY AND PHYSIOLOGY

The phrenic nerve arises from the fourth cervical nerve with branches from the third and fifth, passes around the lateral border of the scalenus anticus muscle and, crossing its anterior surface to its mesial border, descends behind the clavicle between the subclavian artery and vein into the mediastinum through which it reaches the diaphragm.

There are many variations in the origin, course and accessory nerves which are present in a large percentage of cases and frequently give difficulties not only at operation but also in the degree of paralysis obtained. Goetze (205), in a study of 25 cadavers, came to the conclusion that simple phrenicotomy would have been unsuccessful in 68 per cent. In order to obtain complete paralysis of the diaphragm, Goetze advised cutting the nerve to the subclavius in addition to phrenicotomy. He found accessory phrenic branches running in or parallel to the subclavian nerve in a large percentage of cases. He also found accessories running with the ansa hypoglossi. The subclavian nerve arises from the outer cord of the brachial plexus and considerable anatomical dissection is necessary for its exposure.

Felix (166) described the numerous variations of the phrenic both as to accessories and course, and advocated exairesis or avulsion of the nerve. Most of the accessories join the phrenic within a distance of 11 to 13 cm. from the level at which it crosses the scalenus anticus and, therefore, if that much of the nerve is avulsed, one can feel assured of having interrupted any secondary pathways.

Many others have studied the varied anatomy of the phrenic nerve. Ruhemann (466) corroborated Goetze's findings in dissections of seventeen cadavers in which he found accessories in eleven. Five of these were through the subclavian nerve. He also reviewed the literature of the relations of the phrenic nerve to the subclavian vein and other large vessels and found descriptions of the nerve passing through the subclavian vein or in a groove on its wall. He described 14 cases of his own in which the phrenic, with its accessory, formed a sling around the subclavian vein which could very easily have been lacerated during an avulsion. Von Gossnitz (209) and Pons Tortella (427) have described such a sling around the internal mammary artery and the latter author has seen one around the transverse cervical artery. Yano (582) studied 220 phrenic nerves in cadaver dissections and found 94 had accessories through the subclavian nerve and 40 had accessories originating in a spinal nerve.

Kutamanoff (298), in 200 cases, found a triple nerve twice and a double nerve 69 times. He found accessories in 25 per cent but subclavian branches in only 3 per cent. Plenk (424) and Matson found accessories 29 times in 48 cases and a double phrenic 8 times in 112 dissections. Quarti (435), in a careful study of 160 cases, found the phrenic originating solely from the fourth cervical nerve in 51 cases. There was a branch from the third cervical in 3 cases, from the fifth in 96 cases and from both third and fifth in 10 cases. There was anastomosis with the subclavian nerve in 40 cases, with the suprascapular nerve twice and with the ansa hypoglossi once.

Berla (45), in 28 cadavers, found accessories in 13, twice from the hypoglossal nerve. Lutzendorff (327) found 4 cases with both spinal and sympathetic accessories. Aycock (21) found accessories in 65 per cent of 130 dissections, while Fisher (175), in 36 phrenicectomies, found accessories in 13 (in 5 of these the accessories were multiple), and a double phrenic on one occasion. Decker (119) reported accessories in 30 per cent of 72 cadavers, mostly from the subclavian nerve, while Locchi (317) reported 71 per cent in 50 cadavers. Zannelli (589) has reported a bilateral double phrenic nerve and Moore (399) cited a case with five phrenic nerves on one side.

Ernst (160) believed that return of function was due to regeneration through an accessory and cited a case of Schulze in which motion returned following phrenicectomy. Resection of the subclavian nerve at a second operation produced a complete permanent paralysis.

Avulsion of from 11 to 13 cm. of the phrenic nerve is usually sufficient to break all accessory branches; if the accessory only joins the main nerve near the diaphragm, the removal of the entire length of the nerve is necessary for complete paralysis. Salomon (472) collected 6 cases of anastomosis near to the diaphragm and reported one of his own.

The diaphragm is the most important muscle of respiration. It is situated between the thoracic and abdominal cavities. It is composed of muscle fibres which arise from the circumference of the thoracic cage and pass upward and inward to form a central tendon. Anteriorly, the diaphragm arises from the dorsal surface of the ensiform cartilage and on either side from the inner surfaces of the six lower costal cartilages. Posteriorly, it originates from the lumbar vertebrae by means of two crura which form a tendinous arch giving origin to the muscle fibres. The diaphragm completely separates the thorax from the abdomen except for several openings through which pass the aorta, the oesophagus and the inferior vena cava.

Jansen (260) and Strauss (522) found that the phrenic nerve in mammals is the only motor nerve to the diaphragm, which is a muscular organ and undergoes the same degenerative changes when its motor nerve is severed as any other muscle. Studies of these degenerative changes appearing after phrenicectomy have corroborated the findings of both Jansen and Strauss.

Experimental work by Andrei (16), Schlaepfer (483), Felix (167) and Higgins (245) has proven that following phrenic interruption, atrophy begins within a few weeks and progresses until complete degeneration has occurred, about the third or fourth month. This atrophy is uniform throughout the entire half of the organ and extends to the edges of the muscle.

Ricci (447) believed that the edges were inervated by the lower intercostal nerves because in four post mortems he found that the muscle fibres at the circumference had not undergone atrophy. Felix (cited by Graham) believed that the portion of the diaphragm beneath the twelfth rib was innervated solely by the twelfth intercostal muscle. He came to this conclusion from examination of a 6 month embryo. Kiss and Ballon (286), after very careful anatomical and histological research were of the opinion that the intercostals supplied only sensory fibres to the edges of the diaphragm and the phrenic was its sole motor nerve. Stanbury (514) confirmed the findings of Kiss and Ballon. In eleven post mortems from three weeks to six years following phrenicectomy, he found no evidence of intercostal innervation, the diaphragm having degenerated uniformly into a whitish membrane of parchment-like thinness.

Although complete degeneration occurred, Ken Kure (280) believed that the muscle retained its tone due to sympathetic innervation through other nerves. Shimbo (503) and Aoyagi confirmed Ken Kure's findings and stated that cutting the phrenic led only to an inactivity atrophy and that for true degeneration of the musculature, the sympathetic fibres must be severed. W. Felix (167), on the other hand, believed that the tone which the diaphragm maintained after cutting of the phrenic nerve was not derived from sympathetic innervation but was due to surrounding mechanical forces such as the pulmonary tension, the thoracic wall musculature and the intra abdominal pressure. Galan (191) found complete atrophy after phrenicectomy and felt that, if there were any collateral motor innervation from intercostals or accessories, it was insufficient to maintain either trophic conditions or motor functions. In spite of muscle cell degeneration, the tensile strength of the fibrous organ is approximately 50 per cent greater than that of the normal muscle (Meade (349)). Coombs (103) showed experimentally that the vagus played a rôle in the regularity of diaphragmatic contraction.

EFFECT OF DIAPHRAGMATIC PARALYSIS

Respiration. The muscles which effect respiration are the scaleni, intercostals and diaphragm. When the diaphragm becomes paralyzed, there is a compensatory increase in action of the other muscle groups. This has been found by Gale (193), Cassines (88), Castelli (91) and Roith (460). Experimentally, Dunner (142) showed that the minute volume on the operated side was not diminished as compared to the unoperated one and believed that the diaphragmatic paralysis did not put the lung at rest because of increased apical activity and paradoxical diaphragmatic movement. Lemon (308), experimenting with dogs, could find no change in the external respiratory movement of the operated half of the thorax, no change in capacity for exercise and no change in the intrapleural pressure. Hoover (248, 249, 250), on the other hand, found that the action of the intercostal muscles was antagonistic to that of the diaphragm and, after paralysis of the diaphragm, there was a definite compensatory increase in intercostal activity. Head (233) showed that the discrepancy between Lemon's and Hoover's findings was due to the fact that long narrow-chested dogs did not have an increase in intercostal activity, while the broad-chested animals did. He also found an increased respiratory movement in a majority of patients who had diaphragmatic paralysis. Eizaguirre (155), on the contrary, believed that the lower ribs use the normal diaphragm as a base for their expansion during inspiration and with a paralyzed diaphragm cannot expand as well.

The experimental work has been done on animals with normal intercostal musculature and it must not be overlooked that many patients with pulmonary tuberculosis have a marked atrophy of their respiratory muscles on the affected side. Guglielmetti (216) found by means of the Baglioni Pneumograph that after phrenicectomy, the apical region of the chest will have increased movement provided there is no tuberculosis of the apex of the lung. If tuberculosis is present in the apex, there is no increase in movement in this area. Also, with total pleural adhesions, there is no increase in respiratory motion. Schnippenkotter (486) believed that the atrophied musculature of a patient with pulmonary tuberculosis could not compensate for loss of diaphragmatic action.

By means of the Baglioni Pneumograph, Roccas (454) measured the apical respiratory curve before and after phrenicectomy and compared it with the clinical result. When there was a permanent moderate increase in respiration there was a good clinical result. When the increase was only temporary the clinical result was temporary. When there was no change in respiration or an extreme increase there was no clinical result. He attempted to explain these results on the basis of compensatory action of healthy lung tissue in the neighborhood of the disease process and, coincident with this increased respiration, an improvement in circulation with better blood supply to the affected area.

Cavazutti (92) found the vital capacity increased in five cases and decreased in five. He felt that the increased capacity was a good prognostic sign since the other lung was more efficient due to lessening of toxemia and that a decreased capacity was a poor sign because it was evidence that the compression was affecting good pulmonary tissue.

Whether or not there is a change in costal activity, clinical and experimental studies have shown that there is a definite decrease in those functions which depend upon respiratory movement. Werner (573), in a study of 20 cases, found a decrease in vital capacity in all; a decrease in tidal air in 19. There was no change in oxygen consumption due to a better utilization of inspired air. Oyamada (409) found a diminution in respiration and decreased gas exchange which returned to normal in five days. Gianotti (199) also found a decrease in pulmonary ventilation. Pazzagli (416) experimentally found a decreased respiratory function after phrenicectomy but this decrease was not as great as that found after scaleniotomy or intercostal neurectomy.

Wilson (577), using the statistics of other authors, found that more than 60 per cent of the respiratory volume could be accounted for by costal activity. Therefore diaphragmatic paralysis could only reduce respiration by approximately 40 per cent.

Various pulmonary segments. At first glance, diaphragmatic paralysis would be expected to have its greatest therapeutic effect upon the adjacent pulmonary tissue. Stuertz's original indication was for lower lobe disease. Results, as a general rule, do give the greatest percentage of successes in lower and middle lobe lesions. O'Brien (395) found that 46 per cent of upper lobe cavities were closed by phrenicectomy, 62 per cent of middle lobe and 80 per cent of lower lobe. Naegeli (382) and Schulte-Tigges, Bacmeister (25), Baer (26) and Zehner (590) had their best results in mid-zone cavitation, while Zadek (638), Gullbring (219) and Ahlenstiel (2) found their greatest percentage of cures in lower lobe processes.

Experimentally, Bigger (56) showed by insufflation of the bronchial tree with bismuth subcarbonate that stimulation of the phrenic nerve caused a somewhat greater change in bronchi of the lower lobe than of the upper lobe. If this can be used as a measure of respiration, then the diaphragm affects the lower lobe more than the upper but the difference is so slight it probably has no effect in ordinary respiration. Sprawson (512), by means of lipiodol in the bronchi, determined that after phrenicectomy the movements of the base of the lung are absent, those in the middle lung field are lessened and the apical region is not affected.

The great majority of tuberculous cavities occur in the upper lobes. That diaphragmatic paralysis could and did have a definite therapeutic effect upon apical lesions was demonstrated experimentally and clinically. Orsos (405) showed by means of a model that the action of the diaphragm had a direct effect upon the apex of the lung and believed that its paralysis had just as great an effect in placing the apex at rest as it had on the lower lobe. Loeschke (318) also believed diaphragmatic movement and tone had a direct effect upon the apical region and this effect was greater in the asthenic type with pointed apices.

Fornet (180) described a case with an X-Ray shadow which extended outward from the hilus. During elevation of the diaphragm, due to paralysis, this shadow moved upward toward the apex and when the diaphragm returned to normal the shadow also resumed its previous position. Fornet felt that this demonstrated the effect of the diaphragm upon the upper part of the lung. He (181) believed that phrenicectomy had an effect upon the apex not only in the healthy lung but also in a lung containing fibrosis and disease at the apex as well as apical pleural adhesions.

Schulze (493) believed that vertical pulmonary tension was exerted from apex to diaphragm through the hilus and the ligamentum pulmonale, which is composed of fibrous ligaments connecting the pulmonary hilus with the central tendon of the diaphragm. Diaphragmatic movements are transmitted directly to the hilus and through it to the apical regions. Diaphragmatic paralysis causes a relaxation of the ligamentum pulmonale and a cessation of movement and thereby rest and relaxation of the apex are accomplished.

Selective collapse has been demonstrated by Purce and Clarke (434). In 35 out of 61 cases, the diseased area of the lung showed contraction while the healthy areas retained their original volume; in 10 of the 61, the healthy areas showed contraction (contra-selective collapse). All of these were in upper lobe disease. Van Allen (554) also demonstrated selective collapse with phrenicectomy comparable to the selective collapse occasionally obtained with pneumothorax. This selective effect is probably due to the presence of active fibrosis in the diseased area which causes a shrinking of this part of the pulmonary tissue. To compensate for this decrease in volume of pulmonary tissue, there is an emphysema of the healthy pulmonary areas.

Cough and expectoration. Most authors have reached the opinion from clinical observations that cough and expectoration are facilitated following diaphragmatic paralysis. Bettmann (52) believed that cough and expectoration are accomplished in great part by the abdominal musculature and that this effect is more easily exerted through a paralyzed flaccid diaphragm. Clinically, Sauerbruch and Dunner found cough and expectoration easier.

Carlson (86) and his associates refuted this opinion by experiments on dogs. They found that lipiodol was removed more slowly from the paralyzed side than from the normal side and the ability to cough foreign bodies from the bronchi was impaired by diaphragmatic paralysis. Carl (85) believed that phrenicectomy would decrease the ability to expectorate. Lambert (301) found the same result, clinically.

Pulmonary pathology. The pathological changes in the lung following phrenicectomy were demonstrated in dogs by Pomodora (426) who found after two months that there was a marked venous stasis and proliferation of connective tissue with presence of reticulo-hystocytes. These findings are similar to those after collapse by pneumothorax. Biasini (55) studied the effect of various collapse procedures on the lungs of rabbits. Phrenicectomy caused a perivascular fibrosis similar to that obtained by more drastic collapse methods but which developed more slowly.

Riccitelli (449), in autopsies on 3 cases who died three years after phrenicectomy, found marked fibrotic changes on the operated side, not only in previous tuberculous areas but also in non-diseased pulmonary tissue. He believed this fibrosis due to circulatory changes in blood and lymph systems.

Bettini and Celotti (51) found a congestion and desquamation of alveolar epithelium filling the alveoli, and a peribronchial and perivascular proliferation producing an initial fibrosis. These changes could be found in animals two months after phrenicectomy. Weber, Jacobson and Holcomb (568) suggest that this alveolar desquamation may be a factor in producing a greater degree of anoxemia, which is important in the formation of fibrosis and which also checks the growth of tubercle bacilli.

Intrapleural pressure. Haight (223) measured the intrapleural pressures in cases with pneumothorax before and after phrenicectomy and found an increase of 1.5 cm. to 3.5 cm. (average increase of 2.4 cm.) of water in six cases. This increase occurred in some cases in spite of a movable mediastinum, a portion of collapsible lung and a mediastinal herniation. Head reported an increase of intrapleural pressure in one case while Lemon (308), in experiments on dogs without pneumothorax, found no change in the pressure after phrenicectomy.

Venous blood pressure. Injury to sympathetic nerve fibres is considered the cause of the change in venous blood pressure. Lusena (326) found that the venous pressure rose immediately after operation and in 90 per cent of the cases was still elevated one month later. Vasilesco (555) observed a rise in venous pressure independent of an elevation of the diaphragm and thought it to be due to anastomosis between phrenic and sympathetic nerves. Raimondi (437) found a similar rise in pressure in 13 cases. Brea and Ferrari (68) found a rise in venous pressure which persisted longer than other changes.

Laufer (305) noticed that in some cases after phrenicectomy there was a rise in venous pressure, in others a fall. A third group showed no change. In his experiments upon dogs, he found that a phrenicectomy, by means of a cervical approach, consistently caused a fall in venous pressure (in contradistinction to the rise found by the previous authors). When done through a thoracic approach, there was no change in the venous pressure. He felt that the changes accompanying the cervical phrenicectomy were due to injury to sympathetic fibres which does not occur when the nerve is avulsed in the thorax. Laufer alone found a drop in venous pressure after phrenicectomy.

Blood supply. Following phrenicectomy, there is a definite increase in blood in the lung. Whether this is due to the decrease in lung mobility, to the loss of the pumping action of the diaphragm, or to a direct effect upon the blood vessels is a question that has not been definitely decided.

Wolff and Klopstock (581) showed that the lower lobes normally had a greater supply of blood than the upper lobes and felt that collapse therapy redistributed this blood thereby increasing the supply to the apical regions. By animal experimentation, Andrus and Wilson (17) found a 25 per cent increase in blood flow in the collapsed lung while Vallone (553) demonstrated a hyperemia which he ascribed to stasis in bronchial and pulmonary vessels.

Donati (134) thought that injury to sympathetic fibres during phrenicectomy caused increased blood supply which he demonstrated by a rise in temperature of bronchial air on the operated side. Margaria (337) confirmed this work. Belli (39) found in animal experiments that phrenic stimulation caused a decrease in lung volume and avulsion caused an increase which was due to a dilatation of the blood vessels and increased blood supply.

Oyamada (408), alone, found that in animals the blood volume flow of pulmonary circulation was reduced 15 to 20 per cent after operation but returned to normal in a few days.

Development of the thorax. Clinical observations in children following phrenicectomy have shown that there are no anatomical deformities appearing which could be attributed to diaphragmatic paralysis. Harrenstein (229) reported scoliosis in two infants who were born with paralyzed diaphragms, due to brachial plexus injury. Both children also had complete paralysis of the arm of the affected side and this may have been the prime factor in the development of the spinal curvature. Reichert (445) showed that diaphragmatic paralysis caused no change in shape or growth of the thorax in growing puppies.

MODE OF ACTION OF DIAPHRAGMATIC PARALYSIS

Various theories have been proposed to explain the therapeutic effect of a paralyzed diaphragm upon pulmonary tuberculosis. Elevation of the diaphragm, loss of normal diaphragmatic movement, loss of muscular tone with resultant relaxation, and an effect through the tearing of sympathetic fibres which anastomose with the phrenic nerve have all been suggested as the means whereby benefit occurs.

Elevation of diaphragm. A rise in the diaphragm may reduce the lung volume by as much as one-sixth to one-third. The average rise is approximately 4 to 6 cm. O'Brien's (395) average rise was 3 cm. with a maximum elevation of 9 cm. Rautureau (439) had an average rise on the right side of 7.83 cm. and on the left of 3.96 cm. Marked elevations as high as the second rib have been reported by Puder (432), Uebelhofer (543), Kenner (282), Pruvost (431) and Ulrici (cited by Roloff). Lindberg (315) believed that there was an initial rise of approximately 3 cm. followed by a secondary rise of 2 cm. occurring up to 90 days. This may be followed by a tertiary rise. He stated the amount of elevation has a definite effect upon the result and that elevations less than 4 cm. do not give favorable results. On the other hand, Hein (242), and Naegeli and Heymer (380) injected novocaine into the phrenic nerve and found that the immediate rise was just as great as it was seven months after the nerve had been avulsed.

The elevation is usually more frequent (Cooper (104)) and greater on the right side, although Schwatt (499) found a slightly greater rise on the left. The length of nerve avulsed up to 12 cm. has a definite influence upon the degree of elevation of the diaphragm. Rautureau (439) found that removal of greater lengths had no further effect upon the rise.

There are three important factors which have a direct influence upon the height to which a paralyzed diaphragm will rise: (*a*) the amount of muscular degeneration and atrophy which the diaphragm undergoes (dependent upon whether any accessory motor nerve fibres have escaped injury during the avulsion); (*b*) intraabdominal pressure (dependent upon the tone of the abdominal musculature and the pressure in the gastro-intestinal tract); (*c*) fibrosis in pulmonary tissue.

Lunkevic (325) stated that the result is definitely dependent upon the elevation and Matson (344) believed the result more dependent upon the rise in the diaphragm than upon the rest produced. Broga (73) and Castelli (90) agreed with the above in that the elevation is of importance.

That a rise of the diaphragm is not necessary for a good effect has been stated by Toussaint (541), Welles (571), Zucali (593), Pigeon (420), Landgraf (303), Berard (42), Behrens (37), Baillet (29) and Morelli (369). Furthermore, in large series of cases, the beneficial results do not run parallel to the amount of diaphragmatic elevation. Graf (210), Dumarest (137) and Huber (253) stated that improvement is more dependent upon the tendency to fibrosis than upon the rise of the diaphragm, and Anderson (15) found that benefit was not dependent upon the elevation.

Rest. Loss of normal diaphragmatic movement is considered by some to be of great importance in the aid afforded to healing. The inspiratory tug of diaphragmatic contraction plays a great part in respiratory motion and, as has been shown by Schulze (493), this movement is transmitted through the Ligamentum Pulmonale to the hilus and the entire pulmonary field. Hager (222) felt that the rest and relaxation obtained were of more importance than the actual collapse. Schnippenkotter (485) also believed in the rest theory and felt that the atrophied intercostal muscles did not compensate for lack of diaphragmatic motion. He taught patients to breathe abdominally after phrenicectomy and thereby minimize any thoracic movements.

Neuhofer (388) and Dunner (143), on the other hand, believed that diaphragmatic paralysis did not afford real rest to the lower lobe. Mobility was still present as was evidenced by the presence of respiratory breath sounds and the paradoxical diaphragmatic motion.

Relaxation. Beside the loss of motion, the loss of tone plays a part. The lung is an elastic organ and always in a state of tension. This tension is naturally dependent in great measure upon the rigidity and stability of the surrounding structures. Therefore, any lessening of tone of the diaphragmatic musculature must aid in decreasing the intrapulmonary tension. This relaxation of pulmonary tissue is beneficial to the cure of the tuberculous process.

Sympathetic innervation. Others believe that the main action of phrenicectomy is due to the interruption of sympathetic nerve fibres with a corresponding effect upon the pulmonary circulation. Yano

(582) described a definite anastomosis between the phrenic nerve and the sympathetic nervous system while Rousseau and Michel (464) found that one-third of volume of the phrenic nerve was made up of sympathetic fibres.

Belli (39) stimulated the phrenic nerve electrically and found a decrease in lung volume which he considered due to vasoconstrictor fibres in the phrenic nerve. He therefore felt that avulsion of the phrenic causes a vasodilatation which is the beneficial factor in the operation. Donati (134) also believed that the phrenic and sympathetic were communicating and found in experiments on rabbits that there was an increase in temperature of the bronchial air on the operated side due to increased blood supply.

Sympathetic nervous system action has also been considered as an important feature of phrenicectomy by Bonafe (62), Bodungen (59), Brinkmann (72), Delmas, (124) Ronzoni (463), Baccarani (23) and Sergent (502). Donadio (133) found definite evidence of sympathetic nerve connections with the phrenic, both in the cervical region and through the coeliac plexus.

It must not be forgotten that in many instances the paralysis of the diaphragm may have been given unjustified credit for the improvement which may have occurred. Baer (26) had 8 cases in which phrenicectomy was not followed by paralysis of the diaphragm. Healing occurred in 4 of these cases which results would substantiate the theory of benefit from removal of sympathetic nervous system impulses.

Herczog (244) also has shown that in a series of over 400 cases approximately 29 per cent had no paralysis or change in position of the diaphragm. In other words, phrenicectomy had no mechanical effect upon the lung. Nevertheless, approximately 25 per cent of these cases showed a definite improvement following operation. This was a higher percentage result than that which occurred in the entire series.

TECHNIQUE

The exposure of the phrenic nerve in the neck is, in experienced hands, a comparatively simple procedure. The patient lies flat on the back with the neck slightly extended and the head turned away as far as possible from the side to be operated. For the exposure of the nerve, a horizontal incision about 1½ to 2 inches long, parallel to and approximately 1½ inches above the clavicle, may be used. A vertical incision directly over the posterior border of the sternomastoid muscle is preferred by some. After incising skin and platysma muscle, the posterior border of the sternomastoid is retracted medially. This exposes a pad of fat which lies between the posterior surface of the sternomastoid and the anterior surface of the scalenus anticus muscle. Dissection of this fat pad exposes the scalenus anticus upon which the main phrenic nerve can usually be found.

Ordinarily, it is possible to confine the dissection to an area mesial to the external jugular vein but occasionally, it is necessary to tie and sever this vessel. If the exposure is limited to the area immediately over the anterior surface of the scalenus, there is very little danger of injuring other nerves or tearing any large vessels. The transverse colli vessels cross the scalenus just above the level of the clavicle and can be retracted without injury.

After the nerve has been isolated, it is anaesthetised and either cut, crushed or avulsed; simple skin closure is sufficient. In order to prevent pain, due to isolating the nerve, Rummelhardt (467) places a sponge dipped in 0.5 cc. of a 10 per cent cocaine solution upon the nerve immediately after its exposure. Broga (74) uses electrical stimulation for identification of the nerve. The patient takes a long breath when the phrenic is stimulated.

The size of the incision and the amount of dissection necessary is in a great measure dependent upon the type of operation which is to be performed. For simple phrenicotomy or for avulsion, a very small incision may suffice for in both these procedures only the main phrenic nerve need be exposed. A half inch incision is deemed sufficient by Delaney (122) who also uses specially designed retractors to fit into this small wound. Finochietto (172) uses a 10 mm. incision and Chaton (99) a 0.5 cm. incision over the posterior edge of the sternomastoid. Bethune (50) fits the patient with a necklace before operation and then places the incision so that it may later be covered by an ornamental piece of jewelry. On the other hand, if a search is to be made for accessories, which is important when simple crushing is done, then a longer incision with exposure of the cervical roots is necessary.

To expedite the avulsing procedure, nerve strippers have been devised by Steinke (516) and Martin (340), while a special avulsion forceps with a tip projection has been advocated by Proctor (429) and Mercer (353). Washburn (563) designed an avulsion forceps with serrations placed longitudinally so that there was less chance of the nerve slipping.

Even in the most apprehensive patients and in children, it is rarely necessary to use any other anaesthetic than local, novocaine infiltration (Guleke (218)). Killian (283) believes avertin definitely contraindicated in any operation affecting the respiratory system because of its tendency to diminish respiration. On the other hand, Koller (291) used it in 7 cases with no untoward results; one of these was a very cachectic patient with markedly diminished respiratory surface.

Although it is customary to perform the operation upon patients who are under rest treatment, Tamarin (530), Tisi Netto (538) and Magri (335) have reported cases in which paralysis was induced while the patient was ambulant. Magri reports cavities closed in 4 out of 15 cases. Anikin (18) reported 100 phrenicectomies on ambulant patients.

TESTS OF DIAPHRAGMATIC PARALYSIS

Immediately upon the successful interruption of phrenic nerve impulses, the corresponding half of the muscle loses its normal mobility. In the absence of diaphragmatic adhesions, there is usually an immediate elevation of the paralyzed muscle which varies from 1 to 3 cm. These changes may be seen by fluoroscopic examination performed a few minutes after operation.

A rise in the diaphragm does not always occur at once. In fact, in a small percentage of cases with successful paralysis, an elevation does not occur at all. The absence of normal diaphragmatic movements is the best evidence of interruption of motor nerve impulses. Normally, the diaphragm moves downward upon inspiration and upward upon expiration. When paralyzed, all motion may be lost and the muscle may remain immobile. More frequently, the paralyzed musculature moves under the influence of the pressure changes and muscular forces around it. Occasionally, one sees what appears to be minor fibrillary contractions on the paralyzed side. These are probably movements transmitted from the other half of the diaphragm or from the cardiac impulse. The most common movement to be observed after phrenic interruption is what is known as paradoxical motion, i.e., the diaphragm moves upward upon inspiration and downward upon expiration. This is due to the increase in the negative intrathoracic pressure during the onset of inspiration. This increased negative pressure causes the flaccid diaphragm to be drawn upward; the intraabdominal pressure acting from below adds to the upward force. Similarly upon expiration, the diaphragm is forced downward by the positive pressure developed in the thorax at the onset of the expiratory phase. Ordinarily, this paradoxical motion of the paralyzed diaphragm is easily observed under the fluoroscope because it is accentuated by the normal motion of the contralateral side.

Bittdorf (cited by Milani (361)), suggested the following test to accentuate the paradoxical motion. The patient closes his lips and nostrils tightly. He is then instructed to inspire deeply. This causes a marked increase in the negative intrathoracic pressure resulting in an exaggerated paradoxical rise in the paralyzed diaphragm.

When diaphragmatic mobility returns after a temporary paralysis, the muscle may be observed to contract in various segments before the normal unified motion reappears. When phrenicectomy is combined with artificial pneumothorax, it may be more difficult to determine the presence or absence of paralysis. The normal hemi-diaphragm on the pneumothorax side is occasionally pushed downward and after paralysis occurs it may not ascend higher than the other half. Vadone (548) stated that if the muscle is paralyzed its edge appears clear and sharp on inspiration while if there is no paralysis it appears irregular due to contractions. Where there are no adhesions paradoxical motion is always present.

When a small exudate complicates an artificial pneumothorax combined with phrenicectomy, the Kienbock phenomenon occurs: the diaphragm is seen to rise over the level of the fluid on inspiration. When the lower thorax is widened during inspiration there is a lowering of the fluid level. At the same time there is an increase in the negative intrapleural pressure which draws the flaccid diaphragm upward above the level of the effusion. When the pleural effusion is large the fluid level rises upon inspiration due to elevation of the paralyzed diaphragm.

AIDS TO DIAPHRAGMATIC PARALYSIS

Various methods have been used to enhance the effect of a paralyzed diaphragm. These are all in the nature of diminishing respiration on the operated side. Einis (153) uses bandages and pressure over the lower ribs in phrenicectomies which have not been effectual, while Foix (177) and Jullien (270) keep the patient lying upon the operated side for as long as one year postoperatively. Foix also raises the foot of the bed 15°.

Balice (31) believes that if calcium is injected intramuscularly in combination with phrenicectomy a better fibrosis and calcification occurs. Cholette (101) applies an abdominal binder and has the patient lie on the operated side for three to four months after operation, with the foot of the bed elevated. Kochs (288) found a greater decrease in vital capacity when adhesive strapping was applied after phrenicectomy.

In addition to postural and mechanical methods of enhancing the value of phrenicectomy, various operations have been proposed to be used in conjunction with diaphragmatic paralysis. Sato (476), in 1913, first suggested section of the scaleni muscles in the treatment of early apical tuberculosis and J. Alexander (9), in 1929, suggested the possibility of the method being used in conjunction with phrenicectomy and intercostal neurectomy.

The three scaleni muscles arise from the transverse processes of the third, fourth, fifth, sixth and seventh cervical vertebrae and pass downward in the neck. The scalenus anticus inserts into the scalenus tubercle of the first rib, the medius into the upper surface of the first rib, and the posticus into the outer surface of the second rib. By anchoring the first and second ribs at the onset of inspiration, they permit the upper three intercostal groups to draw their respective ribs outward. With the scaleni cut, the upper three ribs and manubrium move downward on inspiration. Aycock (22) has shown that this decreases apical volume by 40 per cent.

Kochs, Els and Junkersdorf (289), in 1930, tried the procedure on monkeys and found it to be technically possible and not dangerous.

Applying the operation to patients, they obtained favorable results. Gale and Middleton (192) advocated its use as an aid to phrenic block and Fisher (176) found its greatest value in patients in whom phrenicectomy had previously been performed without satisfactory result. Aycock (22), in a series of 70 cases, thought that scaleniotomy plus phrenicectomy gave much better results than phrenicectomy alone. Kochs (289), in 12 cases, produced negative sputum in 3, and disappearance of cavity in 3. Clyne (102) reported further improvement in 12 out of 22 cases in which phrenicectomy had previously been done and improvement in 25 out of 41 cases in which both procedures were done at one operation. Cetrangolo (95), Meyer (355) and Giauni (201) have also reported favorable results. In contradistinction, Brown and Atkinson (77) came to the conclusion in 8 cases that scaleniotomy was of no added value.

To scaleniotomy and phrenicectomy, Harms and Grunewald (227) added resection of the first rib in order to further increase apical collapse. This method had originally been proposed by Loeschke and Rost (318). Lauwers (306) not only resected the first rib at the time of performing scaleniotomy and phrenicectomy but also performed an apicolysis as far as the third dorsal vertebra.

Redaelli (443), in 1928, resected the second, third and fourth ribs from sternum to anterior axillary line in conjunction with diaphragmatic paralysis and Monaldi in 1933 reported 14 cases operated upon in the following manner: 1st stage, Phrenicectomy and Scaleniotomy; 2nd stage, Resection of large anterolateral pieces of fourth to the eighth ribs; and 3rd stage, Resection of third, second and first ribs with apicolysis. He believed the first stage reduced the vertical diameter of the chest and the latter operations the horizontal diameter. Takeda (529) also used scaleniotomy and phrenicectomy in conjunction with resection of the upper three ribs. Durante (147) went a step further in nerve resection and added resection of the long thoracic nerve to scaleniotomy and phrenicectomy. He believed the serratus magnus to be a respiratory muscle, aiding the outward movement of the ribs. He cut Bell's nerve in 28 cases while performing scaleniotomy and phrenicectomy.

In view of the fact that there are some who believe that the intercostal muscles compensate for diaphragmatic inactivity by increasing costal respiration, it has been suggested to paralyze the intercostal muscles by either resection or alcoholization of the intercostal nerves in combination with phrenicectomy.

Warstat (562), in 1916, showed by experiments on animals that resection of the intercostal nerves produced a definite decrease in respiration. Bonomo (65), in 1927, resected the first eight nerves in combination with phrenicectomy. Alexander (9), in 1929, advocated intercostal neurectomy in combination with phrenicectomy but over a period of 6 years, Strieder and Alexander (524) had only used the procedure 22 times with the following results: in 20 patients followed one to six years, 3 were cured, one arrested, 10 improved, 1 unimproved and 5 dead. In 14 cases, the improvement was sufficient to permit of a later thoracoplasty. Lunardi (323) used alcohol injection of the intercostals in conjunction with phrenicectomy.

Recently Kugelmeier (297) has suggested the use of pneumoperitoneum in conjunction with diaphragmatic paralysis. He performed a phrenicectomy upon a patient and later decided to use pneumothorax. In error the air was injected into the peritoneal cavity and caused a subdiaphragmatic air pocket. Because of the excellent clinical result obtained, Kugelmeier proposed the method as one of therapeutic value. In view of the fact that pneumoperitoneum has been known to have a good effect upon pulmonary tuberculosis due to elevation of the diaphragm, it is not surprising to find its effect increased by a paralyzed diaphragm.

TEMPORARY PARALYSIS

Temporary diaphragmatic paralysis by means of freezing, alcohol or novocaine injection had been used in tetanus for many years before Stuertz advocated cutting of the phrenic nerve for treatment of pulmonary tuberculosis. It is only in the last few years that temporary paralysis has been advocated instead of permanently excluding diaphragmatic action. Crushing of the nerve has become the most popular method.

Crushing of the nerve or phrenemphraxis, as it was termed by Yates (583), usually causes a paralysis of from four to six months. Its use has been advocated by Alexander (11), Beardsley (35), Behrens (37), Brea (68) and many others. The advantages are that if later partial thoracoplasty or bilateral therapy is required, there will be a return of function of the operated half of the diaphragm. That part of respiratory function which was excluded by the original operation may be necessary for satisfactory breathing. Furthermore, there is the general opinion that if a phrenicectomy is to be of value, it will have shown definite improvement within six months and then, if desired, a permanent paralysis may be induced.

There are others who believe that practically all temporary diaphragmatic paralyses must later be converted into permanent ones. Even Alexander, who advocates crushing, states that 20 per cent must be reoperated. O'Brien (396), Naegeli (381), and Fisher (175) state that practically all temporary paralyses must be reoperated later. Hughes (254) advocates tying a black silk ligature around the nerve to aid in later recognition, while Sagaz (471) places a drop of dye on the nerve. At the second operation, either another crushing or a complete avulsion may be done.

Numerous cases in the literature cite an activation of the lesion upon return of diaphragmatic activity, as late as one to two years after avulsion. Therefore, were a good result to be obtained in six months one would still hesitate to permit the diaphragm again to start to function. Roloff (461) claimed that in 6 to 8 per cent of cases a permanent paralysis ensues even after temporary crushing. Naegeli and Schulte Tigges (381) cited a case where function never returned, although only a crushing had been performed.

A transient paralysis of the diaphragm has been effected by means of novocaine in order to observe the effect. Goetze (203) used novocaine injection to cause a two to three hour paralysis in operations upon the diaphragm. Henschen (243) injected the phrenic nerve near the heart when operating upon the diaphragm. Wegele (569) and Kroh (296) used novocaine to relieve hiccough and the spasm of tetanus. Hein (242) injected novocaine and then observed rise, movement and respiratory functions. He then decided whether or not to cause a paralysis either temporary or permanent. Naegeli (380) used the same procedure. If he found a marked lessening of respiratory function without a rise in the diaphragm, he felt there would be danger should a later rise occur. Under these circumstances he believed operation should be abandoned. This test is of great importance in bilateral therapy.

Temporary paralysis of from three to four months has been obtained by freezing, either with carbon dioxide snow or ethyl chloride (Kirschner (285), Eisenstaedt (154) and Fisher (173)).

Alcohol injection has also been advocated for temporary paralysis with an effect lasting from three months to one year and occasionally longer (Sagaz (471), Matte (345), Cordey (106)). For this lengthy paralysis, 5 cm. of nerve are injected with absolute alcohol. De Winter (578) advised a temporary paralysis with alcohol at the end of pneumothorax treatment, while favorable results with alcohol have been reported by Morin (372) and Michetti (357). Rodet (456) originated a technique for alcohol injection of the phrenic nerve at the dome of the diaphragm. He combined this with injection of the lower intercostal nerves.

Jullien (271) believed that the results from diaphragmatic paralysis were so uncertain that a phrenicectomy should rarely be performed. Sacrificing healthy pulmonary tissues is not a rational procedure and he therefore advocated alcohol injection of the phrenic nerve in preference to permanent paralysis.

RETURN OF FUNCTION

During the last few years there have been reports of return of diaphragmatic function in spite of an apparently successful exairesis. In view of the fact that some of these cases have a reactivation of their lesion, following resumption of diaphragmatic motion, the possibility of the necessity for a secondary operation must always be borne in mind. Sonnenfeld (509) was the first to report, in two cases, a complete return of function three years after successful exairesis had been performed.

Schulze (492) cited a case from the Munich Clinic in which there was a return of function in nine months, in spite of an apparently good exairesis. At a secondary operation, the subclavian nerve was isolated and removed, with complete paralysis. Noack (391) stated that he knew of cases where, in spite of removal of 10 to 30 cm. of nerve, function returned after one and one half to two years with reactivation of the original lesion. Jeanneret (261) cited two similar cases and stated that to reparalyze, the new nerve should be sought for in the old scar and a radical Goetze operation performed. Derscheid (129) claimed that cavities reopen more frequently after phrenicectomy than after pneumothorax and felt that the cause might very well be mechanical, due to return of function.

Bernou (47) reported return of function in 9 out of 24 cases and cited Rautureau as observing it in 24 out of 25 cases. Magrassi (334) reported return of function in a child, fourteen months after operation, while Wiese (576) has seen it in children six months to two years after removal of a long section of the nerve.

Schwatt (500) reported return of function in 11 out of 131 cases after phrenicectomy. In 7 of these 11 cases more than 10 cm. of nerve had been avulsed. Wirth (579), in a follow up on 185 cases (out of a series of 600), found 24 cases where the function of the diaphragm returned to normal after it had been definitely paralyzed for a considerable time. The lengths of nerves avulsed were not stated. Nevertheless, the temporary paralysis had had a good effect in 20 out of the 24 cases.

Oekonomopoulo (401) in 1932 found return of function in 7 cases in a series of 125 and in 1934 (402) reported 2 more cases in the same series. Zucali (592) found a return of function after eight to nine months in 4 out of 19 cases and Baer (26) reported return of movement in 13 cases. Matson (343) found no return of function if at least 10 cm. of nerve were removed. In a follow up on 11 cases with less than 10 cm. avulsed, there was a revival of mobility in three cases.

INDICATIONS

The indications for phrenicectomy have undergone many changes since Stuertz' formulation. First proposed for bronchiectatic lesions, they were soon broadened to include pulmonary tuberculosis of the lower lobe. As soon as the institution of the Felix exairesis and the Goetze radical phrenicotomy assured the attainment of a definite permanent diaphragmatic paralysis, the operative procedure became world wide in its usage. In a short time not only lower lobe lesions but middle and upper lobe disease as well were being treated. It was used to influence exudative as well as productive pathological processes. It was considered of value as a "test operation" before thoracoplasty, as an aid in preventing aspiration pneumonia in the lower lobe during upper thoracoplasties, as a means for symptomatic relief in bilateral disease processes, as an aid in eradicating empyema cavities, as an aid to pneumothorax and numerous other indications.

It can readily be seen that a simple therapeutic measure which had so many indications in a disease so widespread as pulmonary tuberculosis, would soon come into popular favor. Thousands upon thousands of diaphragms were paralyzed in the hope that this new-found panacea would live up to expectations. Experiences of careful observers eventually showed that many phrenicectomies had been performed in vain.

In some clinics the use of diaphragmatic paralysis has gradually become more and more restricted, while in others it still flourishes as a method of collapse therapy which is used on almost every admission.

Age and sex. Phrenicectomy has been performed upon patients in all age groups. Roloff (462) has shown the results upon discharge and follow up in the following table.

	NUMBER OF CASES	CLOSED CASES	
		Discharge	Follow up
years		*per cent*	*per cent*
7–15	5	20	60
15–20	22	18	18
20–25	36	11	17
25–35	70	14	24
35–45	57	21	32
Over 45	41	24	24

He feels it is significant that while pneumothorax gives the best results below the age of 35, phrenic operations give better results above 35 years than from 15 to 35 years.

Above 50, phrenicectomy must be used with considerable care. In the presence of emphysema and myocarditis, diaphragmatic paralysis may cause marked dyspnoea and be a source of great discomfort to the patient.

The results of phrenicectomy as regards sex are the same as in other forms of collapse therapy. Female patients show slightly greater benefits from treatment. This is probably due to the fact that they are better able to maintain their rules of therapy and do not return to their occupations prematurely.

Race. The type of pulmonary lesion which develops in negroes is not the sort which is benefited by phrenicectomy or other surgical measures. Gaines (190) however, reported 25 phrenicectomies in negroes with improvement in 44 per cent and felt that the results could be favorably compared with those in the white race.

In children. Collapse therapy in children had been confined to the use of pneumothorax up to 1926. In that year, Wiese (575) reported the first series of 45 cases of phrenicectomies in children from four to fifteen years. Most of them were from twelve to fourteen years of age. Twenty-five were in conjunction with pneumothorax and twenty as independent operations. Of these twenty, the results in ten were excellent and seven satisfactory. Cases with good results were also reported by Ravina (440), Baer (26), Harms (226), Magrassi (334), Carrau (87), Cantonnet Blanch (82), Bindschedler (57), Stricker (523), Zadek (587), Perera (417) and Bruin (78).

Fechter (165) reported 20 cases where phrenicectomy was used in conjunction with pneumothorax but follow up was not sufficiently long for evaluation of results. Simon (504), in 1928, cited 35 cases, 12 of which were as independent operations. In 1930 (505), he had increased his series to 47 cases, 16 of which were independent operations. He came to the conclusion that it was of little value except in conjunction with pneumothorax. Wiese (576), in 1931, cited a series of 205 cases of phrenicectomy in children with only one accident (a tear in the apical pleura resulting in pneumothorax but the final result was good). He felt that the action of phrenicectomy in children was the same as in adults.

English (156) reported 12 cases of the adult type of tuberculosis in children treated by phrenicectomy, 7 of which were independent operations. Of these 7, the results were excellent in 2 and satisfactory in 1. Osorio (407) used alcohol injection in children and reported 33 per cent cured in 14 cases. Eschbach (161) has reported a phrenicectomy in a child of ten months with closure of a tuberculous cavity.

All observers agree that the indications for phrenicectomy in children are the same as in adults. Only the adult type of tuberculosis with cavitation and fibrosis is favorably influenced. Accidents are rare, as in adults, but the results are still open to question.

As an independent procedure. A. Frisch (187), in 1921, claimed priority in suggesting that phrenicectomy would be valuable as an independent therapeutic measure. The majority of those who used the procedure as Frisch suggested, found that although it did not live up to first expectations it nevertheless had some value (Alexander, J. (10), Bacmesiter (25), Beatty (36), Berard (40), Dunner (144), Graf (210), Harms (228), Head (234), Horing (251), Johns (266), Lobmayer (316), Naegeli (382), O'Brien (396), Punschel (433), Sachs (469), Sadowski (470), Schlack (482), Schwarzmann (496), Thomsen (536) and Wirth (579)).

As in every other form of collapse therapy, the evaluation of the results obtained by diaphragmatic paralysis is dependent upon many factors. It is evident that the surgeon who performs a phrenic crush upon every "minimal lesion patient" in order to ascertain its value, will become a staunch advocate of the procedure, for his results will undoubtedly show a large percentage of "cures." If one were to subtract those "cures" which are obtained in that type of case upon bed rest alone the results would not be exceptional. Similarly, if the operation is performed upon patients with a chronic extensive process the end results must be poor.

The method and duration of rest treatment which accompanies the period of diaphragmatic paralysis are also of great importance. Although the procedure is called "independent phrenicectomy" it is in reality an adjuvant of bed rest therapy. And if the basic rest period is not maintained it undoubtedly will have a deleterious effect upon the phrenicectomy results.

The duration of observation as well as the method of post operative follow up will both be important factors in the evaluation of the results obtained. Some symptomatic improvement follows practically every phrenic nerve operation. The active hospital service and the sanatorium which keeps its patients for a relatively short period of treatment will naturally discharge a great percentage of improved cases. If the follow up is conducted by questionnaires filled out by the patient or his family physician without benefit of X-ray and sputum examination, the reports will be without value.

It is the differences in the above factors which cause the wide variations in the results obtained by phrenicectomy when used alone. (See Tables I and II.) In contradistinction to those who found value in the procedure Boneo (63) had negligible results in 107 cases. Denk (125) believed that it was used more often than indicated and its value as an independent operation was still not settled.

Ernst (159) found only 15 cures in 185 cases. Gravesen (212), in 1928, found the operation indicated only 30 times in four years and these were in conjunction with some other form of therapy, but in 1935 (214) reported 153 independent operations with 38 cures. Kan (276) found it a purely palliative measure, while Losio (321) claimed that it had no value as an independent procedure. Noack (391) used the procedure only if pneumothorax, plombe or plastic could not be done, and Sauerbruch (480) found no cures in 60 cases. Lehmann (307) felt it was only of value as an aid to other procedures.

As a primary operation. There are even some who believe that phrenicectomy gives such favorable results in certain types of lesion that it should be preferred to pneumothorax (Head (235)). On the ground that the complications of phrenicectomy are practically nil, while with pneumothorax, embolus, fluid and empyema occur, they prefer to use the less dangerous procedure at once. Up to recent years, pneumothorax had always been considered as the most efficient method of collapse therapy and phrenicectomy had been tried only where pneumothorax was impossible. J. Alexander (7), in 1924, first suggested the use of primary phrenicectomy, and Naegeli (378) concurred in this opinion. Head (234) did a phrenicectomy in 75 early cases and compared the series with a control group placed on bed rest. Those with phrenicectomy showed much better results than the control series. O'Brien (398) believed that diaphragmatic paralysis should be instituted before pneumothorax in minimal lesions and found that this will prevent many minimal lesions from progressing. Pleininger (423) believed that the diaphragm acts through the base of the lung upon the hilus region and advised phrenicectomy for hilus cavities before pneumothorax is tried. Punschel (433) found that soft cavities near the periphery should be treated by phrenicectomy in preference to pneumothorax. In opposition to the above, Morin (370) performed phrenicectomy in a series of cases in which pneumothorax was indicated and could have been carried out. He came to the conclusion that similar cases treated with pneumothorax gave a more favorable result.

In various types of lesions. In the early years of its use, phrenicectomy was considered of value in order to convert an exudative lesion into a fibrotic one. At one time, H. Alexander (5) and Bacmeister (24) advocated it for this purpose. Diamanti (131) reported six cases of lobitis without cavitation in which the results after phrenicectomy were remarkable. Experience later showed that fibrosis was not the result of collapse methods but due more to the bodily reactions to the invading organism. Phrenicectomy, like other forms of collapse therapy, was of value only in those patients who could show a fibrotic tendency. It has been rather definitely decided that certain types of cavities are amenable to influence by paralysis of the diaphragm. It is quite evident that old, thick-walled, rigid cavities can not be closed by a minor procedure such as phrenicectomy. Early, small or medium sized, thin-walled or moth eaten cavities, especially those with little disease in the surrounding pulmonary tissue, are the types in which there is the best chance for a favorable result.

Furthermore, the best results are to be obtained in the "cold" type of case which is afebrile, not losing weight or strength, and in which the cavitary process is either stationary or progressing very slowly.

Relative to segment involved. The original indication for lower lobe lesions has been substantiated by the accumulated experience of practically all observers. Graf (210), in a large series of cases, found that all middle or lower lobe lesions were cured or improved, while Punschel (433) found that a higher percentage of lower lobe lesions became sputum negative than of upper lobe lesions. That it has its greatest usefulness in lower lobe disease has been stated by H. Alexander (5), Campbell (81), Davies (117), Dunner (144), Ferrari (171), Forgue (179), Gullbring (219), Moskaljov (374), and Thearle (532).

The great majority of cavitary lesions occur in the upper lobes. As a treatment of cavitation in this region, phrenicectomy has been advocated by many. The results are not as good as in lower lesions but, nevertheless, it has been used successfully by Akif Schakir (3), Berard (42), Dumarest (140), Freund (183), Jessen (263), Lobmayer (316), Naegeli (381), Oekonomopoulo (400), Schwarzmann (497), Sonnenfeld (510), Tapia (531), Wirth (579), O'Brien (395), as well as many others.

In bilateral disease. In the early days of collapse therapy only those cases which were either strictly unilateral or in which there was only minimal disease in the contralateral lung were treated. In the last decade the collapse treatment of bilateral disease has increased with tremendous strides until today we find all types of therapy being applied to both lungs simultaneously: bilateral pneumothorax, bilateral phrenicectomy, bilateral partial thoracoplasty, bilateral pneumothorax with phrenicectomy on one side (Scholz (487)), pneumothorax on one side and phrenicectomy on the other, thoracoplasty on one side with pneumothorax on the other. In fact, Maendl (331) reported a case of phrenicectomy and total Brauer thoracoplasty on one side with a pneumothorax induced later on the other side.

Landgraf (303) and Pigger (421) used phrenicectomy on the more active side in bilateral disease with favorable results. Chmeljnitsky (100), on the other hand, used phrenicectomy in 27 cases with bilateral disease and found that 18 showed increased activity in the other lung. O'Brien (396) reported 288 phrenicectomies in patients with bilateral disease. In 26 per cent there was complete healing of both lungs, in 53 per cent the contralateral lesion improved. Schuberth (491) felt that in bilateral upper lobe cases with the mediastinum drawn to the more affected side a phrenicectomy on that side produced bilateral improvement in the following manner: the rise in the diaphragm permitted the mediastinum to return to its normal position thereby relaxing the contralateral lung as well as the pulmonary tissue on the side operated upon.

Maendl (330), in 1928, described a case of bilateral tuberculosis treated by pneumothorax on one side and phrenicectomy on the other. He claimed it to be the first so described in the literature. But Borchardt (66) had reported 8 such cases in 1927 with good results in 4. Frigerio (184) felt that contralateral pneumothorax was indicated as a support measure if phrenicectomy caused a marked mediastinal shift with symptoms.

In presence of adhesions. Mobility of the diaphragm before operation would appear to be a necessity in order to expect results from its paralysis. The presence of adhesions around the diaphragm is, therefore, one of importance. Bodungen (59), Johns (267), Margulis (338), Naegeli (378), Steiger (515), and Anderson (15) believed that when they are present only an effect on the lower lobe could be obtained. Head (232) stated that in the presence of diaphragmatic adhesions, paralysis is definitely contraindicated. He felt that with adhesions present, the median pull of the diaphragm, which is antagonistic to the intercostals, is definitely increased to such an extent that there may be a paradoxical movement of the lower ribs downward and inward on inspiration. If such a diaphragm is paralyzed, the intercostals will be able to act unimpeded and there will be a definite increase in respiratory movement.

In spite of the apparent uselessness of paralysis of a fixed diaphragm, if the other indications for the operation were present, one should not be deterred from a trial. Zehner (590) and Milani (360) felt that adhesions have no effect on the rise in the diaphragm nor paradoxical movement. Many observers feel that the loss of muscular tone and the absence of the inspiratory tug, even without a rise in the diaphragm, is sufficient to give a beneficial action. Roloff (462) and Kremer (294) saw good results even with a fixed diaphragm. Haensel (221) felt that a diaphragmatic paralysis had an effect upon pleural adhesions and aided in their absorption. He cited two cases where pneumothorax had been impossible in a few attempts. After phrenicectomy a pneumothorax was easily induced. One must not forget that frequently it requires many trials before the free pleural space is found.

Whether the presence or absence of fibrosis in the interlobar fissure aids or lessens the effect of phrenicectomy has been the subject of controversy. Bodungen (59) believed that phrenicectomy could have no effect on the upper lobe were a thickened interlobar fissure attached to the parietal pleura. On the other hand, Kremer found that the operation only affected upper lobe lesions if the interlobar fissure were thickened and there were a fibrotic tendency, while Steiger (515) believed that interlobar fibrosis had no effect on the value of phrenicectomy.

Kremer (295), by means of an x-ray Kymograph, as described by von der Weth (574), determined which parts of the lung were affected by the diaphragmatic movement and thereby decided whether paralysis of the diaphragm could be of value.

As a test operation. In the earlier attempts to use thoracoplasty in the treatment of pulmonary tuberculosis, phrenicectomy was used as a preliminary operation in order to test the ability of the other lung to withstand the increased burden which it would have to bear after collapse (Alexander, H. (5), Berard (42), Bordet (67), Sauerbruch (479)). In the last few years this indication for phrenicectomy has been definitely abandoned. Firstly, in many cases in which the contralateral lung did well after phrenicectomy, it nevertheless showed progression after thoracoplasty. Huber (253) did test phrenicectomies in 21 patients previous to thoracoplasty. Although the test apparently showed the opposite lung to be capable, nevertheless 11 of these died from contralateral disease after thoracoplasty. Furthermore, phrenicectomy on the right side with its corresponding rise in the liver was a hindrance to a later good collapse by rib resection (Jessen (265), Kohlhass (290), Denk (125)). In the evolution of collapse therapy, many partial thoracoplasties are taking the place of the complete operations done previously and most surgeons today believe that if a partial thoracoplasty over the upper lobes is contemplated, it is desirable to keep the usefulness of the lower lobe intact. Furthermore, Gravesen (214) has found a higher operative mortality and a lower percentage of bacilli-free patients following upper thoracoplasties which were preceded by diaphragmatic paralysis as compared with patients with functioning diaphragms.

For prevention of post operative pneumonia. Early thoracoplasties were performed by removal of the lower ribs at the first stage and the upper ribs at the second operation. When the procedure was reversed and the upper ribs resected first it was thought that if the diaphragm was paralyzed previous to the operation there would be less chance of occurrence of post operative complications in the lower lobe (J. Alexander (8), Davies (116), Stuertz (525), Ulrici (544)). In addition to the above use, phrenicectomy also found favor for a time as an adjunct to minor surgical procedures performed upon the upper lobe. Nissen (390) used phrenicectomy previous to apicolysis in order to prevent aspiration into the lower lobe. Kremer (293) advised the use of phrenicectomy previous to the insertion of a plombe, not only for preventing aspiration pneumonia but also to reduce the size of the cavity. Sattler (477) used it before inserting a plombe because he believed that it aided the paraffin to remain in its correct position.

Holst and Semb (246), on the other hand, made a careful study of post-operative atelectasis in their upper thoracoplasties by means of serial X-rays. In 64 cases with an immobile diaphragm (56 due to phrenicectomy), atelectasis occurred 43 times or 67 per cent. In 27 cases with normal diaphragmatic movements, postoperative atelectasis occurred only 3 times. Inasmuch as they believe that atelectasis is a predisposing cause of postoperative pneumonia, the dangers of a paralyzed diaphragm are evident.

The clinical work of Gravesen and Holst has shown fairly conclusively that a paralyzed diaphragm increases the incidence of pulmonary complications. Experimentally, the evidence is equivocal. Nakao (383) found that foreign bodies in the trachea are more easily aspirated into the lower lobe of the operated side; injections of staphylococcus gave a lower mortality in animals with phrenicectomy and the pathological changes were less on the operated side. Balice (30) gave massive doses of tubercle bacilli to dogs and found that diaphragmatic paralysis had a favorable effect on the circumscribed lesions which developed. On the other hand, Razemon (441) found that intravenous injections in rabbits and guinea pigs gave a greater number of miliary abscesses on the operated side, but in these experimental animals the paralyzed diaphragm rose and then immediately sank lower than the normal side.

Carl (85) injected tubercle bacilli intravenously following phrenicectomy and found less disease occurring on the side operated upon. Lemon (310) found no difference in the incidence of aspiration pneumonia on the two sides after unilateral phrenicectomy in animals.

Foote and Spies (178) immobilized one side of the chest in guinea pigs by means of phrenicectomy, intercostal neurectomy and rib splinting. They then inoculated the animals with tubercle bacilli and found an equal distribution in most cases. Where there was a difference in the distribution, it was in favor of the immobilized side.

In presence of extra pulmonary lesions. As in other forms of collapse therapy, a phrenicectomy which results in an improvement in the pulmonary lesion will also have a beneficial effect upon tuberculosis situated in either the larynx or intestines. Wasowski (564) showed that a phrenicectomy had a good effect upon laryngeal tuberculosis not only through improvement in the general condition but also by diminishing coughing and rendering the sputum free of bacilli. Lesions in other parts of the body are hematogenous in character and are influenced by phrenicectomy only through general bodily improvement.

In hemoptysis. In spite of the voluminous literature on diaphragmatic paralysis as a therapeutic agent in pulmonary tuberculosis, very little has been written as to its value in hemoptysis. It is difficult to evaluate the importance of any treatment of hemoptysis for so many hemorrhages cease with and without active therapy.

Pribam (428) cited four cases in which persistent hemoptysis stopped following phrenicotomy and Frisch (185) reported a similar effect. Jessen (264) reported one case in which pneumothorax stopped hemoptysis temporarily and when it recurred, a phrenicectomy was performed with complete cessation of bleeding. Raimondi (436) used the procedure in a similar manner. Petrin (419) claimed diaphragmatic paralysis to be of value in 15 cases of hemoptysis. Bertotto (49) reported two cases with good results. Edwards (151) reported that hemoptysis ceased in four cases after phrenicectomy and Cecchini (93) reported three such cases. Bronfin (75) stated that in 56 patients hemorrhage was controlled in 27, improved in 8, remained the same in 6, and became worse in 15.

Others have reported the occurrence of hemoptysis shortly after phrenicectomy and thought it due to the passive congestion which occurred. Schurch (494) advised the avoidance of phrenicectomy in cases with tendency to hemorrhage.

In spontaneous pneumothorax. Spontaneous pneumothorax, occurring either during the course of artificial pneumothorax therapy, or into a virgin pleural space, is very often a fatal complication and usually a serious problem to handle. If a tension pneumothorax ensues, due to a valve-like action at the site of lung perforation, the air must be aspirated. If a secondarily infected empyema occurs, drainage must be done. Goldschmidt (206) and Weiss (570) have used phrenicectomy in this condition in order to lessen the thoracic movements, especially the inspiratory phase. Each reported a successful case with closure of the fistula. Both cases were of tension pneumothorax treated by aspiration of air and later phrenicectomy.

In diabetes. Since the use of insulin in diabetes, there is no longer any great need to separate the cases of pulmonary tuberculosis with diabetes from those not so complicated as far as collapse therapy is concerned. Gergely (197), Labbe (299) and Izzo (258) have reported good results from phrenicectomy in cases complicated by diabetes and have shown that diabetes is no contraindication to phrenicectomy.

During pregnancy. Phrenicectomy has been performed during pregnancy as a method of treatment of a coincidental pulmonary tuberculosis. Apparently, a paralyzed diaphragm does not seriously affect the expulsion of the child and in some cases may have a good effect upon the pulmonary lesion. Castagna (89), Migliavacci (358) and Vercesi (556) have reported good results from diaphragmatic paralysis performed during pregnancy, both as regards the immediate symptoms and lessening of danger of puerperal spread. Duryea (149) believed that the raised diaphragm of pregnancy should be maintained during the puerperium and reported a case where a bilateral phrenicectomy was carried out after delivery (first operation two days postpartum and second side eight days later), with symptomatic relief.

Roloff (462) believed that breathing space already lessened by intraabdominal pressure should not be further reduced by phrenicectomy. Armanini (20) used phrenicectomy in one case of pregnancy where pneumothorax was impossible. There was an improvement in the lung condition. Delivery was not hindered but there was a reactivation during the puerperium.

As aid to artificial pneumothorax. Although there is still considerable question as to whether phrenicectomy has an independent value, there is practically universal agreement that as an aid to pneumothorax, diaphragmatic paralysis is an important therapeutic measure.

Frisch (186), in 1922, was the first to report the use of the combined procedures in cases in which, because of basal adhesions, the pneumothorax was ineffective. Maendl (328) also advocated its use in this type of case. Zadek (584, 585) found the combination of sufficient value to use phrenicectomy before every pneumothorax. He found that refills were required less frequently (40 per cent in pneumothorax and only 8 per cent in pneumothorax plus phrenicectomy), exudates appeared less often and, at the end of treatment, less expansion of the lung was required in order to fill the hemi-thorax.

On the other hand, Purce (434) and Clark found that in 178 cases there was an increased tendency to obliterate the pleural space when pneumothorax was augmented by phrenicectomy. This made frequent refills a necessity. Vadone (550) used the combined procedures in all ambulant cases but most observers only add phrenicectomy when especially indicated (Hebenstreit (236), Ulrici (544), Brieger (71), Sadowski (470), Schwarzmann (496), Gravesen (212)).

Brieger (70) did not believe in using phrenicectomy as an aid to pneumothorax because it neutralized the Holzknecht phenomenon. In artificial pneumothorax, the mediastinum usually shifts toward the collapsed side on inspiration. This allows of greater expansion of the good lung and therefore greater arterialization of blood. In the presence of a paralyzed diaphragm, this mediastinal shift does not occur; the flaccid muscle is drawn upward instead. Brieger felt that this may have been the cause of dyspnea due to anoxemia. Deist (121), on the other hand, did not find dyspnea occurring with the combined procedures.

Unverricht (546), H. Alexander (6) and Ulrici (544) advised against the use of phrenicectomy with every pneumothorax because it would lessen the ability to treat the contralateral side should it later become diseased. This opposition may be removed by the use of temporary paralysis. Maendl (332) warned that in the presence of a paralyzed high diaphragm, refills must be carefully done so as not to puncture the diaphragm.

Where there is a good lateral pneumothorax with apical and basal adhesions, Jessen (265), Alwens (14) and Omodei-Zorini (404) advocate the combined use. As a means of lessening lung expansion at the termination of pneumothorax, it was used by Dundee (141), Omodei-Zorini (404), Goetze (204), Redaelli (442), Jessen (263), Pollock (425) and many others. In the occasional case where the lung did not expand at the cessation of pneumothorax therapy, Ulrici (544) and Vadone (549) paralyzed the diaphragm so that its rise would aid in closing the pleural space. De Winter (578) advised its use at the termination of pneumothorax only in questionable cases where reactivation was feared. Etcheverry (162) successfully used diaphragmatic paralysis to prevent exudates which appeared after each refill.

Besides being of value in adherent apical cavities where the lower lobe is attached to the diaphragm, phrenicectomy is a great aid to pneumothorax in upper lobe cavities which are suspended by a string or band adhesion, even though the diaphragm is free. Slavin (507) and Gillick (202) found that if the tension of the diaphragm toward the hilus is removed, the cavity will be drawn upward toward the adhesion and thereby compressed. This will even occur without an elevation of the diaphragm. Isnardi (257) believed that diaphragmatic paralysis not only aided pneumothorax when there were vertical adhesions, but was also of value in the presence of horizontal adhesions.

In empyema. The two great problems in the treatment of empyema occurring during the course of pulmonary tuberculosis are to counteract the pleural infection and to obliterate the pleural space. The development of empyema is frequently dependent upon the occurrence of a bronchial fistula. Paralysis of the diaphragm has been used in order to lessen lung movements, thereby aiding the closure of a small fistula.

In obliteration of the pleural space, phrenicectomy is of great value. The rise in the diaphragm reduces the size of the thoracic cavity at its widest point. Furthermore, the elevated position aids in the gradual reexpansion of the lower lobe. An obliterative pleuritis, developing in the angle between the diaphragm and the lower lobe, tends to draw the atrophic muscle upward, as well as the pulmonary tissue outward toward the chest wall.

If a small bronchial fistula is present near the base of the lung, it may possibly be closed by the adhesion of the diaphragm to the visceral pleura. Sundberg (527) has reported the cure of a small basal empyema, with both bronchial and cutaneous fistula, by means of diaphragmatic paralysis. Dufour (136) also obliterated a basal empyema, with bronchial fistula, by means of phrenicectomy.

Where external drainage has been instituted because of the occurrence of secondary infection and the lung is bound down by a thickened visceral pleura, a large dead pleural space persists. This must be closed by surgical measures. Extensive thoracoplasty is usually required; a paralyzed diaphragm is of great value in obliterating the lower part of the cavity.

Jones (269), Hedblom (239), Harven (230), Geisemeyer (196), Melchior (351), Wolff (580), Ritter (453), Bonniot (64) and Courcoux (106), as well as many others, advocated the use of phrenicectomy to aid in the closure of an empyema cavity. Lambert (300) warned that the diaphragm should not be paralyzed too early in the course of a graded thoracoplasty. The rise in the abdominal contents may prevent a successful lateral collapse of the chest wall. He preferred to perform complete rib removal and then, if necessary, proceed with a phrenicectomy to obliterate the lower angle.

CONTRAINDICATIONS

Phrenicectomy is a minor surgical procedure and there are very few contraindications to the operation itself. In the main, the contraindications have been discussed in the chapter on indications.

Ordinarily, the contraindications to a surgical procedure are those conditions which will be aggravated by operation or lead to a fatal issue. In the case of phrenicectomy, the contraindications must be considered in the light of conditions which experience has proven cannot be benefited by the procedure. If this thought is kept in mind, useless phrenicectomies will not be performed upon hopeless cases. Even though phrenicectomy be a minor surgical measure, one must not attempt its use for pathological lesions which cannot possibly be benefited thereby.

BILATERAL DIAPHRAGMATIC PARALYSIS

Although paralysis of both sides of the diaphragm had been used as early as 1914 for intractable spasm due to tetanus, it was not until 1925 that Curti (108) reported 3 cases in which the procedure was used in the treatment of bilateral pulmonary tuberculosis. A good result was obtained in 2 of these. In 1927, he reported on 6 cases (109). In 5 of these, both sides were operated upon at the same time. One patient who had bilateral exairesis, died ten days after operation because of cardiac failure. The others all had a phrenicotomy with only 2 cm. of nerve removed. Curti could show no cures but all patients had an improvement in their general condition and he stated that the procedure was not a dangerous one. In 1932, he described 10 cases (110). Six died within three years, 3 were fair or well (4 mos., 2 yrs., 5 yrs.) and one was cured after 4 years. He felt that the bilateral operation was also indicated to prevent shifting in the presence of a movable mediastinum (analogous to a support pneumothorax). Thomsen (536) reported a case with a three year follow up, in which there was doubt as to the closure of the cavities although the patient was working.

In 1929, Dunner (146) stated that he believed the procedure was of value just as bilateral pneumothorax had been found useful. Even though Brauer had reported a case where the patient died due to asphyxia, because of a great rise of the diaphragm on both sides, Dunner felt that, inasmuch as the procedure was only used where pneumothorax was impossible, the pleural adhesions would prevent a sudden or great rise in the diaphragm. He suggested waiting a few weeks between operations to see whether the first hemi-diaphragm would rise excessively. He felt that it should not be attempted in fixed, emphysematous chests, or in patients with marked bilateral involvement. Dunner (145) also reported one case in a sixteen year old patient who had had the first phrenicectomy performed at twelve years. There was no change in the vital functions of gas exchange, etc. and respiration was definitely easier than before operation.

Honan (247) also reported one case. One month after a good rise in the first half of the diaphragm, the second side was operated upon. There was no elevation, probably due to emphysema of the lower lobe. The patient was discharged, clinically improved.

Iselin (256) stated that there was no great effect upon respiration even when both sides were operated upon in one stage, and that the procedure was indicated wherever bilateral pneumothorax was indicated but not possible of attainment. He also used bilateral phrenicectomy as an aid to incomplete pneumothorax.

Duryea (149) reported a case of a woman who had a bilateral pneumothorax induced in the sixth month of pregnancy and then had a left phrenicectomy two days after delivery and a right phrenicectomy eight days later; the pneumothorax on the right being maintained with symptomatic improvement.

Schwatt (498) reported one case in which a right phrenicectomy was followed by healing of a cavity in the mid lung field. Eighteen months post-operatively, a cavity developed in the left mid lung field for which a phrenicectomy was performed. Eight months later, the cavity in the left lung was closed but there was a return of function of the right diaphragm with a subsequent reactivation of the lesion in the right lung. Bailey (27) reported two cases of bilateral phrenicectomy. The one for pulmonary tuberculosis was of no value while the second for bronchiectasis was decidedly harmful in that the patient could not expectorate and had to be kept in the Trendelenburg position and died three months post-operatively. Cerkaskij (94) reported 7 cases with an interval of one to four and one half years between operations in 6, and an interval of one month in the 7th. The latter was the only case with a favorable outcome. O'Shaughnessy (406) reported 4 cases of bilateral operation with one death. Lobmayer (316) had one case.

Bilateral diaphragmatic paralysis is a therapeutic measure which has its place in the treatment of pulmonary tuberculosis. It must be remembered that in bilateral pulmonary tuberculosis there is a considerable destruction of pulmonary tissue as well as an atrophy of those accessory muscles of respiration which ordinarily compensate for diaphragmatic inactivity. Before paralyzing the second half of the diaphragm, the effect of the paralysis of the first half should be noted. Temporary paralysis with novocaine at the time of the second operation will provide a clue as to the ability of the cardiorespiratory system to withstand the procedure.

Many observers are still wary of bilateral paralysis. Bodungen (59) believed that it could only add to increased muscular activity including greater demands upon the heart. J. Alexander (10), in 1930, stated that it had not as yet been shown to be "effective or constantly safe."

COMPLICATIONS

The complications of phrenicectomy may be divided into those due to errors in surgical technique and those occurring during or after a faultless operation.

Under the first heading, we have injuries to the thoracic duct, as described by Kleinschmidt (287), Vilardell (557), Mazzetti (348) and Csiki (107). Fortunately, such an injury has a negligible mortality and healing usually occurs without sinus formation. Welles (571) reported one case. Sauerbruch (cited by Roloff) has reported a chylous fistula and Schoff has seen a death three weeks after operation due to chylothorax.

Injuries to the cervical sympathetic have also been reported. These give rise to a Horner's syndrome which manifests itself by myosis, enophthalmos and ptosis of the upper lid. This complication has been observed by Deist (120), Fermin Mas (169), Kennedy (281), Muzzarelli Verzoni (377), Dalto (113), Strain (521), Faniel (163), Anikin (18), Ulrici (545) and Vaccarezza (547). The injury to the sympathetic nerve may be permanent due to its being mistaken for the phrenic, or temporary due to pressure from a retractor. Even the recurrent laryngeal nerve has been injured, causing paralysis of the vocal cord (Apitz(19) and Brunetti (79)). Cetrangolo (97) saw a recurrent laryngeal paralysis following left phrenicectomy, which he thought was due to a mediastinal displacement. Felix (166) has reported injuries to the vagus and Bell's nerve.

Injuries to blood vessels may be due to the fault of the operator or to conditions over which he has no control. Injuries to vessels presenting in the wound are rare but have been reported (Kleinschmidt) and can be ascribed directly to faulty operative technique. H. Alexander (4) reported death from hemorrhage from a branch of the subclavian vein and Stoney (520) reported an injury to the internal jugular vein by a sharp retractor. The tear was successfully ligated. Ulrici (545) had 2 hemorrhages in 1200 operations. Both were controlled. Injuries to large veins in the neck may give rise to air emboli. Such a complication has been reported by Friedrich (cited by Matson (343)), Jehn (cited by Roloff) and Sauerbruch (cited by Graham). On the other hand, the variations in its course, and the accessories of the phrenic nerve, with sling like formations around either the transverse cervical vessels, the subclavian vein, or internal mammary artery, may give rise to injuries to these vessels during avulsion. Also the proximity of the phrenic nerve to the pericardio phrenic artery may cause a hemorrhage, due to tearing of this vessel (Thomopoulos (535)). A death from massive mediastinal hematoma has been reported by Caralps Masso (84). Because of two deaths which he thought due to deep hemorrhages from complete avulsion, Bani (33) changed his technique and removed only 6–8 cm. of nerve. It must not be forgotten that during the universal rush to perform phrenicectomies in almost every type of lesion, many were done on very sick or possibly dying patients, and it is no surprise to find reports of fatal outcomes. For instance, Berg (44) reported death in a patient 6½ hours after operation. Post-mortem examination revealed a pulmonary embolus from a femoral phlebitis, in no way connected with the operation.

Injuries to the apical pleura with development of a pneumothorax may also occur during avulsion. Tearing of mediastinal glands (Grinsfunt (215)) may give rise to mediastinitis and pericarditis. Zehner (591) reported a case of severe laryngeal perichondritis following phrenicectomy. He believed that operative trauma activated a dormant lesion.

Pulmonary complications following phrenic avulsion range from atelectasis to pneumonia and include marked progression of the lesion with occasional fatal termination. It is difficult to evaluate the relationship between the operation and the ensuing progression of the disease or the occurrence of new lesions, for in many such cases the phrenicectomy was undoubtedly performed on very sick patients with progressive disease. Walker (560) and Rodenacker (455) have reported cases of marked dyspnea. Berry (48) collected 13 deaths from pneumonia or progression of the disease in either the operated side or the other lung, and 31 cases in which it was thought the diaphragmatic paralysis had a distinctly bad influence upon the disease process, although the patients survived.

Deist (121) reported 2 cases of lower lobe tuberculous pneumonia occurring on the side operated upon. Loewenthal (319) believed that a severe reaction after phrenicectomy was very likely due to a pneumonia. He observed 5 cases in 350 phrenicectomies with both clinical and X-ray evidence of pneumonia in the lower lobe of the side of the operation. He believed that they were non-tuberculous and due to trauma of the rising diaphragm.

Froehlich (188) saw 4 cases of massive collapse of the lower lobe due to diaphragmatic elevation, while Sarno reported 2 cases of fresh tuberculous infiltration of the lower lobe. Dumarest (139), in spite of careful selection of cases, had 6 to 7 per cent of fresh lesions appearing after operation. Gomez (207), in order to avoid the occurrence of postoperative pneumonia, used anti-pneumococcic vaccines.

A contralateral exudative pleurisy was observed by Ricci (446), Symens (528), Diamanti (132), Montes Valarde (364) and Maendl (333). All of these cases had a favorable outcome.

Deaths from pulmonary oedema were reported by O'Shaughnessy (406), Burnand (80) and Komis (292). Fatal hemoptyses were observed within a few days after operation by Naegeli (379) and Fernandez Garcia (170), but it was difficult to determine the relationship between operation and the subsequent hemorrhage.

Isolated instances of death following phrenicectomy were reported by Chandler (98), Hedblom (238), Kleinschmidt (287), Morone (373), Schnippenkotter (485), Schurch (494), Bronfin (75) and Epstein (157).

Weber (567) reported a death in six days due to cardiac failure because of marked shifting of the heart to the left side after right phrenicectomy. Schrodl (490), using avertin as an anaesthetic, ascribed a death $2\frac{1}{2}$ hours after operation to the use of this drug in a patient with lowered respiratory surface. Miliary tuberculosis, following phrenicectomy, was thought by Patronikola (415) to be due to entrance of bacilli into a torn vessel.

EFFECT UPON THE GASTRO-INTESTINAL TRACT

Numerous isolated reports of severe gastric disturbances, following both right and left diaphragmatic paralysis, have crept into the literature. Nevertheless, large series of cases with careful follow up have shown that, as a general rule, the gastric symptoms which do occur are mild and only transient in character. The symptoms that occur can be ascribed to changes in position of the stomach, duodenum and colon, or to the relaxation of the diaphragmatic crura which encircle the esophagus. Kawana (279), experimenting with dogs and rabbits, found that after phrenicectomy, the tone of the stomach was lessened but gastric emptying and peristalsis remained unchanged and there was no effect on stomach function.

After left phrenicectomy with elevation of the diaphragm, the stomach usually rises, the pylorus is drawn to the left and, occasionally, the colon is drawn upward following the diaphragm (Lichtenstein (314), Ehrenburg (152)). After right-sided paralysis, the pylorus tends to be drawn upward and the stomach assumes a transverse position (Ricci (448)). Roloff (462) as well as Slavin and Kommerell have demonstrated by x-ray the interposition of the colon between the liver and the diaphragm after right phrenicectomy. Occasionally, these changes in position have been so marked that mechanical kinks have caused obstructive symptoms and even volvulus. Such complications have been reported by Berard (43), Noack (392), Durante (148), Cetrangolo (96), Bonafe (61), Lonquet (320) and Paltrinieri (411).

The rise in the stomach which follows a left diaphragmatic paralysis frequently causes the so-called Roemheld complex of bloatedness, nausea, vomiting, palpitation and tachycardia. These symptoms have been observed by Roesler (459), Parade (413), Roemheld (458), Sporn (511), Patronikola (415), Wirth (579), Lowenstamm (322), Raimondi (438), and Berlin (46).

Blask (58) reported a case of cardiospasm and Fromme (cited by Ernst (158)) described stasis in the lower oesophagus following right phrenicectomy but, to the contrary, most observers feel that paralysis of the diaphragmatic crura will cause a relaxation of the cardia (Kaufman (278), Cetrangolo (96), Ernst (158) and Hruby (252)). Sauerbruch corroborated this observation by placing his finger through the cardia both before and after paralyzing the diaphragm. He found a definite loss of muscular resistance after operation. Ballon (32) came to the conclusion that angulation of the oesophagus might occur after phrenicectomy but that there was no experimental evidence that obstruction or cardiospasm occurs.

Postoperative x-rays of the stomach and duodenum have revealed marked changes in form and position of these organs without any clinical symptoms. This has been demonstrated in 23 cases by Zadek (588) and Jahnke (287), and Lichtenstein (314), in 14 right phrenicectomies. Derscheid (127) found changes in the stomach in 68 per cent of cases without symptoms.

Noack (392) believed that the gastro-intestinal complications of phrenicectomy were severe enough and occurred with sufficient frequency to narrow the indications for the operation. Rickers (450) also felt that severe gastric symptoms occurred frequently. When these bad effects were compared with good results, the value derived from the operation was greatly diminished. Contrarily, most reports indicate that the disturbances are usually mild and seldom occur. Ernst (158) saw no symptoms in 179 cases. Wirth (579), in 600 cases, observed only 5 cases of bloatedness. Berlin (46) reports one case with gastric symptoms in 43 operations. Dalla Palma (112) found 3 cases in 63. Roemheld (458), in 143 left phrenicectomies, saw 14 with minor gastric symptoms and only 3 in which they were fully developed. Sporn (511) found symptoms in 3 cases out of 60; Patronikola (415) reported 4 in 124. Ehrenburg (152) found 18 cases with symptoms in 58 left phrenicectomies. In 5 of these, they were slight, in 5 moderate, and in 8 annoying. Bronfin (75), in a review of 183 cases, found gastric symptoms negligible. Sonnenfeld saw no major symptoms in 200 cases and Sachs (469) none in over 150.

The evaluation of gastric symptoms in tuberculosis is difficult. Many patients have unstable digestive powers and are beset with stomach and intestinal disturbances. Jurcev (272) believed that in addition to the actual change in position of the diaphragm, the neurotic element was a great factor in the production of symptoms following phrenicectomy.

EFFECT UPON THE HEART

The change in position of the diaphragm has an effect upon the position of the heart as has been shown by x-ray and electrocardiographic studies. Torelli (539) studied 100 "best" radiographs from 400 phrenicectomies and came to the conclusion that after right phrenicectomy, the length of the heart appeared increased, and after left phrenicectomy the heart appeared raised and broadened with apex beat higher and more lateral. Mecklenburg (350) corroborated these findings and felt that the heart was turned on its dorso-ventral axis, which rotation was also manifest in the electrocardiogram. He found only one case with heart symptoms after right phrenicectomy and a number after left-sided operation. Ballon (32) found electrocardiograms normal except for changes due to rotation of the heart's axis. Jensen (262) confirmed these findings in 19 cases.

Hansen (224) studied the heart tracings in 100 cases before and after phrenicectomy. Her findings agreed with Mecklenburg's and she could find no evidence of conduction delays or of myocardial changes. In spite of these definite changes in heart position, it is uncommon to find cardiac symptoms postoperatively. In 600 cases, Wirth (579) found palpitation 12 times and a vise-like feeling twice. Hecht (237) observed one patient in 24 who developed extra systoles postoperatively, while Sarno (474) reported 2 cases developing rapid pulse after left phrenicectomy. One showed sinus rhythm, the other sinus tachycardia. Cetrangolo (96) cited two cases with marked precordial symptoms. In one, the apex beat was impaired because of its striking against the elevated diaphragm and stomach.

Ritschel (452) performed phrenicectomy on a patient with pulmonary tuberculosis, complicated by congenital pulmonary stenosis. There was no increase in the cardiac symptoms postoperatively.

Mittenleiter (362) felt that an elevation of the diaphragm might have an effect upon the circulation by kinking the inferior vena cava where it passes through the tendinous arch. Furthermore, diaphragmatic movement is thought to aid the return flow of blood to the heart through the great veins.

RESULTS OF DIAPHRAGMATIC PARALYSIS

It has been a very difficult task to correlate and classify the published reports upon the results of phrenic nerve operations in the treatment of pulmonary tuberculosis. Unfortunately, there has been no standard to determine that which is to be considered a "cure" in collapse therapy. Some authors described their results on a basis of whether or not the patient was working. Others used the terms "improved" and "not improved." Some used the presence or absence of tubercle bacilli in the sputum as a criterion of cure and others used the disappearance of the cavity as an indication of a favorable result. If one were to accept only those results which claimed both a disappearance of cavity and a negative sputum (both of which must be present for a "cure"), there would be very few reports which could be tabulated.

Furthermore, follow up periods were not always accurately stated and many results were determined by the findings upon discharge from sanatorium care rather than upon later check up.

Because of all these discrepancies, it was decided to divide the accumulated statistics into two tables. In both tables the entire number of phrenic operations performed is listed, together with the number of cases followed and the follow up period (when stated).

Results of independent phrenic nerve operations

TABLE I

	YEAR REPORTED	NUMBER OF OPERATIONS	FOLLOW UP	NUMBER OF CASES FOLLOWED	INDEPENDENT PHRENICECTOMY					
					Number of cases	Cured	Improved	Same	Worse	Dead
			years							
Acuff (1)	1933	112	1–3	109	112	52	48	7		1
Alvarez (13)	1931	11		11	11	1	2	4	1	3
Anderson (15)	1934	51	1–3	51	24	8	5	1	2	8
Baer (26)	1933	118	½–11		98	20	20			13
Bailey (28)	1934	59	2–5	59	54	16	20	6		12
Basar (34)	1930	52		52	52	19	8			
Bezalel (54)	1934	200			200	28				
Bridge (69)	1929	60	1½	60	60	15	22	13		10
Broga (73)	1932	72	¼–2	72	72	13		24	23	12
Bronfin (76)	1933	183	1–5	183	122	12	56	16	15	23
Cecchini (93)	1930	31		31	31	6		19		
Decker (119)	1933	222	1–5	181	94	25	34	14		21
Delay (123)	1934	74		74	74	8	34	32		
Derscheid (128)	1932	827		827	827	160	343			
Douglass (135)	1933	100	½–3	100	62	21	30	11		
Dworetsky (150)	1933	40	1–6	37	33	2	13	1	8	9
Ernst (159)	1930	185	1–10	137	137	15				94
Frank (182)	1930	100		50	50	8	16			
Geer (195)	1932	114		114	84	29		41		14
Graf (210)	1930	136	2–7	67	67	35	18		3	11
Graham (211)	1935	54	2–3	54	54	5	27	9		10
Gravesen (214)	1935	223	2–10	223	153	38	17	(98 cases)		
Guglielmetti (217)	1934	36			36	21		14		
Gullotta (220)	1931	34	1	30	30	9	11			
Hare (225)	1934	83	1–3	83	83	6	27	50		
Harms (228)	1931	100	8	83	83	5	16		10	52
Hauke (231)	1924	24		22	16		3	6	1	6
Head (234)	1932	75		75	75	28	34	1	5	7
Hegner (241)	1929	30			11	1	9		1	
Horing (251)	1931	56	3	56	56	14	11	21	8	
Huber (253)	1932	32	10	30	30	9	4	3		14
Jones (268)	1933	122	10	122	40	9	22	9		
Kaganov (273)	1928	17		17	17	3	9			4
Lamont (302)	1932	75		75	75	8	53	7		7
Lapin (304)	1934	200			125	6	55	59		5
Leslie (312)	1934	75		75	75	37	26		12	

TABLE I—*Continued*

	YEAR REPORTED	NUMBER OF OPERATIONS	FOLLOW UP	NUMBER OF CASES FOLLOWED	INDEPENDENT PHRENICECTOMY					
					Number of cases	Cured	Improved	Same	Worse	Dead
			years							
Lundre (324)	1932	73		73	73	2				
Marcy (336)	1933	175		161	161	46	48	41		26
Matson (342)	1927	90		90	90	8	55	27		
Maurer (347)	1934	285	3	267	267	43				
Moore (366)	1930	63	2–5		10	2	5	1		2
Mues (375)	1931	65	1–9	65	65	21	8	10		26
Naegeli (382)	1933	57	5	57	57	21		10	5	21
Neddermeyer (385)	1931	100		80	80	9	40	31		
Nehil (386)	1933	654		612	272	90	95	33	14	38
O'Brien (395)	1930	500	4	378	378	191	119	53	15	
Oekonomopoulo (401)	1932	125	½–4	125	125	40	33			
Oeri (403)	1931	67		54	54	20	14	20		
O'Shaughnessy (406)	1932	53		32	32	3	9		7	13
Parfitt (414)	1929	34	5	25	19	6	8		5	
Patronikola (415)	1932	124	10	111	100	4	4	9	4	79
Perret (418)	1925	5			5	1				
Pigger (421)	1926	21		21	21	1	18			2
Proust (430)	1933	202		202	202	21				
Punschel (433)	1932	600	4–10	210	210	21	84	52		53
Purce (434)	1936	300	1–4		88	23	34	18	13	
Rist (451)	1933	200	2–10	200	200	26	16			86
Rodenacker (455)	1927	33	5	33	33	9				11
Roloff (461)	1931	767	2–8	231	231	56		61		114
Sachs (469)	1930	107	1–8	66	66	39		14		13
Sadowski (470)	1933	249	1–6	62	62	34		19	9	
Schakir (481)	1932	31		31	31	12	12			7
Schlack (482)	1932	120	1–2	120	120	75		27		18
Schneiter (484)	1932	29	2–5	29	29	3	15	9		2
Schroder (489)	1926	59			59	20	24			
Schwarz (495)	1933	112	½	51	51	6	20		7	9
Sergent (501)	1934	68		68	68	8				
Sinding-Larsen (506)	1934	153		153	153	55		(98 cases)		
Slavin (508)	1934	68		68	68	17		51		
Steiger (515)	1932	70		70	47	7	5	35		
Steinke (517)	1931	33		33	12	3	3		3	3
Stekelis (518)	1930	166	3	153	153	14	63	28	14	34

TABLE I—*Concluded*

	YEAR REPORTED	NUMBER OF OPERATIONS	FOLLOW UP	NUMBER OF CASES FOLLOWED	INDEPENDENT PHRENICECTOMY					
					Number of cases	Cured	Improved	Same	Worse	Dead
			years							
Thearle (533)	1931	355			256	9	70			
Thibault (534)	1934	45	2	45	37	11	12	14		
Thomsen (536)	1928	130	1–4	74	74	14				
Tillman (537)	1931	38	2–6	38	38	0				
Trojan (542)	1933	58	8	40	40	5	11	1	15	8
Werner (572)	1930	100	3	100	75	34	29	5	7	
		10,567			7,435	1,734				

The cases in which diaphragmatic paralysis was used as an independent operation are then listed separately and the results given.

Table I consists of those cases in which one could judge, from the criteria which the author used, that a definite healing or "cure" had resulted. Undoubtedly, errors have been made in the interpretation of the various standards of healing but in such a large series, the percentage error is reduced to a minimum. In Table II are listed those cases in which the authors used only such terms as improved, benefited, working, etc.

In Table I, only the "cured column" can be considered of importance because, as can be seen, many authors reported their "cures" without giving the various results in the rest of the series. Similarly, in Table II the "improved column" alone can be used for statistical purposes.

It is very evident that the type of patient operated upon has a great effect upon the results obtained. When cures can range from 0 to over 60 per cent, it must be the material that causes the discrepancy in results. Nissen (389) stated that if phrenicectomy cured 60 to 70 per cent of a series of cases many of such cases would have healed without the operation. Roloff's (461) study of permanent end results was very carefully performed upon a group of cases which appeared to be a fair cross section of mixed material. His result, 24 per cent "healed," is similar to the percentage of all the cases tabulated in this compilation and reported as cured.

TABLE II

	YEAR REPORTED	NUMBER OF OPERATIONS	FOLLOW UP	NUMBER OF CASES FOLLOWED	INDEPENDENT PHRENICECTOMY		
					Number of cases	Improved	Not improved
			years				
Ahlenstiel (2)	1933	322	5–10		208	51	157
Alexander (4)	1922	7		7	7	5	2
Alexandrov (12)	1931	25		25	25	13	12
Anikin (18)	1933	100	½	59	59	38	21
Belkina (38)	1928	95	1–5	95	95	61	34
Berard (41)	1929	114	1–6	86	86	41	45
Bogopolsky (60)	1931	34	1–2	34	34	25	9
Caralps Masso (83)	1928	8		8	8	8	
Castelli (90)	1929	100	½–3	100	71	43	28
Chmeljnitsky (100)	1935	135	2–7	135	135	47	88
Dabrowski (111)	1929	55		55	55	17	38
Daniel (114)	1933	478		478	478	81	397
Daniello (115)	1932	53		53	53	23	30
Davies (117)	1928	29	1–2	29	29	12	17
Dumarest (138)	1930	120	1–7	120	120	96	24
Edwards (151)	1928	28		28	28	21	7
Faxon (164)	1931	15		15	15	6	9
Fischer (174)	1923	20	½–2	20	17	16	1
Fuhrmann (189)	1926	4		4	4	3	1
Gammons (194)	1931	31			10	6	4
Gergely (198)	1926	100		71	45	36	9
Giauni (200)	1931	26		26	26	14	12
Gomez (208)	1931	86		58	55	23	32
Hedblom (240)	1932	43		43	43	26	17
Iamandi (255)	1932	240		240	240	120	120
Kahn (274)	1930	102			95	8	87
Kalasnikova (275)	1935	36	1–4	36	23	7	16
Kassowitz (277)	1926	81		81	56	41	15
Leo (311)	1934	41	¼–1½	41	41	28	13
Li (313)	1931	10	2	10	10	6	4
Maendl (329)	1928	100	1–7		45	24	21
Martin, A. (339)	1931	16	1–2	16	16	14	2
Martin, S. (341)	1933	6		6	6	5	1
Matz (346)	1936	233	½–6	233	233	35	198
Menne (352)	1929	14		14	14	13	1
Merkulov (354)	1935	204		204	204	110	94

TABLE II—*Concluded*

	YEAR REPORTED	NUMBER OF OPERATIONS	FOLLOW UP	NUMBER OF CASES FOLLOWED	INDEPENDENT PHRENICECTOMY		
					Number of cases	Improved	Not improved
			years				
Michelsson (356)	1926	64		64	64	34	30
Mikkonen (359)	1931	39		39	39	17	22
Moore (365)	1934	412	4	412	412	370	42
Morelli (368)	1923	18		18	18	18	
Morin (371)	1932	153		153	153	89	64
Murie (376)	1934	138	10	138	138	52	86
Nalivkin (384)	1927	34		34	34	22	12
Nemchenko (387)	1932	30	1–4	30	30	16	14
Pai (410)	1932	100		57	57	45	12
Paolucci (412)	1928	15	3	15	15	10	5
Piollet (422)	1929	32		32	32	11	21
Rehberg (444)	1936	150	2	49	49	35	14
Russel (468)	1934	50	½	46	46	25	21
Sarno (473)	1927	17		17	17	7	10
Scholz (488)	1930	35		35	35	7	28
Schulze (492)	1931	90	2	90	90	27	63
Schwarzmann (496)	1933	330	2–12	244	244	151	93
Spuzic (513)	1930	46		46	46	32	14
Stekelnikov (519)	1929	23		23	23	15	8
Toussaint (541)	1930	339		339	339	189	150
Vainer (551)	1930	102		61	61	45	16
Vitez (558)	1932	360	3	360	360	90	270
Walker (559)	1932	34		34	34	18	16
Wasowski (565)	1934	34		34	17	15	2
Watson (566)	1933	253		116	79	40	39
Welles (571)	1929	300		271	271	173	98
Wirth (579)	1929	600	1–5	185	162	84	78
Yates (583)	1927	94		94	94	77	17
		7,003			5,648	2,837	

17,570 phrenicectomies, as reported by 142 authors have been collected. The results of 78 authors reporting 10,567 operations are tabulated in Table I (Cured, healed or arrested). Of these 10,567 operations, 7435 were performed as independent procedures with 1734 (23.3 per cent) "cures."

The results of 64 authors, reporting 7003 operations, are tabulated in Table II (Improved, working, etc.). Of these 7003 operations, 5648 were performed as an independent measure with 2837 (50 per cent) improved.

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THE INFLUENCE OF THE PITUITARY AND ADRENAL GLANDS UPON PANCREATIC DIABETES[1]

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INTRODUCTION

The concept of diabetes mellitus as a disorder of metabolism secondary to a deficient supply of insulin has become firmly established, largely owing to the observations of Minkowski that total pancreatectomy in the dog led to a condition indistinguishable in many of its features from diabetes mellitus in man.

In spite of the many obvious similarities between these two conditions, i.e., pancreatic diabetes in the dog and diabetes mellitus in man, there have always existed several notable points of difference. These are (a) that in many human cases the degree of destruction of the pancreas is entirely disproportionate to the severity of the disease, particularly if it be remembered that some nine-tenths of the dog's pancreas must be removed before a glycosuria becomes established; (b) a not entirely negligible proportion of diabetics succumb in coma with no demonstrable lesions in the pancreas; (c) the occurrence of glycosuria and other evidences of a disordered carbohydrate metabolism in association with disease of other members of the glandular system, notably the pituitary and adrenal; and (d) total removal of the pancreas in other species is not followed by the same alterations in metabolism that are observed in the cat and dog. Thus, Minkowski pointed out that in the pig and fowl, the diabetes following total pancreatectomy was different from that of the dog. These results have recently been expanded and confirmed by Long and Lukens (1), Lukens (2), and Sprague and Ivy (3). In consequence, we are not in a position to say that total pancreatectomy in man would necessarily produce the same effect as it does in the dog, although both species might have certain features in common.

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From a clinical point of view, many attempts have been made to classify glycosurias into those of a pancreatic and non-pancreatic origin, but an increase in the blood sugar sufficient to produce a glycosuria may arise from a variety of causes, of which a deficient supply of insulin is only one. The net result of these endeavors has been to draw up a set of conditions under which it has been held that a persistent glycosuria either during fasting or after a meal is an indication of the impairment of the bodily processes by which the excess glucose presented to the tissues is oxidized or stored for future use as glycogen. A circumstance in which this inability of the tissues to oxidize glucose has been found has been interpreted as due to an insufficient quantity of insulin, and this in its turn is based upon the total diabetes of a depancreatized dog.

In other words, our present interpretation of human diabetes is based on the premise that this disease is of pancreatic origin and that varying degrees of insulin deficiency result in varying degrees of impairment of the ability of the tissues to utilize glucose, this impairment reaching a maximum in a total inability to oxidize glucose, at which point the condition becomes entirely similar to that observed in the totally depancreatized dog.

This rigid interpretation of diabetes has excluded certain other possibilities, some of which are not entirely new concepts. These are (a) that the processes by which glucose is produced from non-carbohydrate sources, i.e., protein or fat, may become so disordered that the glucose supply outruns the ability of the tissues to utilize it. This might occur even if the insulin supply was normal, or else might be exaggerated by an insulin deficiency. (b) Other endocrine glands might produce hormones whose effect upon the tissues was an inhibition of glucose utilization and whose presence in excessive quantities would obviously indicate by the usual methods that the tissues were not disposing of ingested carbohydrates in the normal manner. Finally, (c) although removal of insulin greatly reduces the capacity to oxidize glucose, yet other effects of insulin removal might be a large factor in the production of the syndrome observed after total pancreatectomy. Thus it is possible that insulin not only accelerates glucose utilization, but also exerts an inhibitory control upon those processes or organs in which glucose formation from non-carbohydrate sources occurs. With its removal from the body, not only are these processes unhindered but at the same time tissue utilization is greatly reduced, partly by the absence of insulin and partly by the presence of other hormones that directly inhibit carbohydrate utilization.

If it be allowed, then, that there exist in the body (a) processes under hormonal control that result in glucose production from non-carbohydrate sources, and (b) processes also influenced by hormones that increase or decrease tissue utilization, then it becomes possible to conceive of a disturbance akin to diabetes which may be produced by disorders of (a) or (b) acting singly or together. Now it will, of course, be readily admitted that the organism does possess means to form glucose when none is available in the diet or during starvation and it also will be agreed that the capacity of the tissues to utilize glucose may vary to a wide degree.

In consequence, it is of extreme importance to investigate the influence of all the glands of internal secretion upon these processes and not to limit our inquiry to the influence of the pancreatic hormone alone upon carbohydrate metabolism.

The purpose of the present paper is to call attention to the fact that evidence already exists that the hormones of other glands of internal secretion do influence carbohydrate metabolism and also that their removal modifies in a striking manner the effects that heretofore have been attributed solely to insulin deficiency. While much work remains to be done, enough facts have been found to indicate that the pituitary and adrenal glands play an important rôle not only in carbohydrate metabolism but also in determining the sequence of events that follows total pancreatectomy.

The effects of hypophysectomy upon carbohydrate metabolism

The importance of the hypophysis in the endocrine system is due not only to the many bodily processes that are subject to the influence of its numerous hormones, but also to the fact that its removal is followed by a striking atrophy of most of the other endocrine glands. Thus, there occurs involution of the gonads, thyroid and adrenal cortex and probably of other glands of internal secretion. Not only do these marked anatomical changes follow hypophysectomy, but of greater interest is the concurrent hypofunction of the organs involved. In consequence, it is not surprising that the metabolism of the hypophysectomized animal exhibits marked deviations from the normal, since it is well known that certain of the endocrine glands that are affected are in themselves of importance in the maintenance of a normal metabolism. The alterations in the metabolism of the hypophysectomized animal may, therefore, be not entirely due to a loss of specific hypophyseal hormones but may, in addition, be contributed to by the combined hypofunction of such organs as the adrenal and thyroid.

As a matter of fact, a comparison of certain features of hypophysectomized animals with those of adrenalectomized or thyroidectomized animals, indicates that they overlap to a considerable degree. Thus, all exhibit increased insulin sensitivity and an increased resistance to the hyperglycemic action of epinephrine. Glucose absorption is retarded and the glucose tolerance exhibits similar anomalies. Fasting causes a marked fall in blood sugar that is seen to its severest extent in fasting hypophysectomized animals in which hypoglycemic convulsions are not uncommon.

The effects of hypophysectomy upon carbohydrate metabolism vary somewhat in different species. Thus, although all species exhibit sensitivity to insulin and a fall in blood sugar on fasting, the ability of the tissues to oxidize glucose as judged by the glucose tolerance curve is said to be increased in the toad and rabbit, but to be decreased or unchanged in the dog and rat. The effects upon protein metabolism are also the subject of conflicting reports. Some workers find that removal of this organ reduces the fasting catabolism of protein, but others contend that it is increased.

It would be unwise at the present time to attempt any full explanation of the changes produced in the processes of metabolism by removal of the pituitary, but these are undoubtedly widespread and of a fundamental character. In considering, as we shall now do, the alterations in pancreatic diabetes produced by hypophysectomy, it should be borne in mind that removal of this organ not only involves the loss of its hormones but also, in consequence of their removal, induces functional alteration in other glands controlling metabolism and probably alters the responsiveness of the tissues to such quantities of these hormones as may remain in the body fluids.

The effect of hypophysectomy upon pancreatic diabetes

The classical effects of total removal of the pancreas from the dog or cat are (1) hyperglycemia and glycosuria that persist during fasting; (2) the nearly quantitative excretion of ingested glucose and the failure of the respiratory quotient to rise above 0.71 after such ingestion; (3) an increased urinary nitrogen excretion both in fed and fasted animals and the establishment of a reasonable degree of constancy between the urinary glucose and nitrogen in animals on a meat diet or when fasted. This ratio is in the neighborhood of 2.8; (4) a marked increase in the acetone body content of the blood and urine, largely in consequence of the increased proportion of fat undergoing metabolism; (5) finally, the development of severe acidosis, coma and death. The period of survival of the dog is from one to two weeks, while in the cat it is rarely longer than five to six days.

The work of Houssay and his numerous collaborators (4) has demonstrated that the above changes are altered to a remarkable degree by removal of the hypophysis. It is immaterial whether this gland is removed before the pancreas or whether the diabetes is already fully established before it is excised. In either case the effect is the same. Houssay first demonstrated the effect of hypophysectomy upon the pancreatic diabetes of the toad but soon extended his observations to the effects in the dog.

The studies carried out by Dr. F. D. W. Lukens and myself along with my various other collaborators have been largely concerned with an investigation in as quantitative a manner as possible of the effects of hypophysectomy and other procedures upon the pancreatic diabetes of the cat. These experiments were undertaken first of all to provide confirmation of Houssay's findings in the toad and dog, and secondly in an endeavor to elucidate some of the mechanisms by which these effects are brought about. The details of the methods we have employed will be found in an earlier publication (5).

The removal of the pancreas from a hypophysectomized cat (or dog) is followed by the following deviations from the diabetes usually observed (table 1):

(*a*) *Survival.* As Houssay and others have found in the dog, the life of the depancreatized cat is prolonged by removal of the hypophysis. There is, however, considerable variation from animal to animal and the length of survival is largely determined by the initial nutritive condition of the animal as well as by its escape from the hypoglycemic episodes that have abruptly terminated the existence of many of our preparations. As table 1 shows, death has occurred from hypoglycemia (due to refusal of food) in as short a time as eight days, while at the other extreme, one animal survived for nearly three months. The ultimate death of even the long-surviving animals is to be attributed to the marked inanition that occurs. This is partly due to the fact that a certain degree of diabetes persists and partly to the digestive disturbances that follow exclusion of the pancreatic juice from the intestine. There is also no doubt that just as the severity of an ordinary pancreatic diabetes is ameliorated by marked inanition, so in these long-surviving, doubly-operated animals part of the improvement in carbohydrate metabolism is to be attributed to the great loss of body weight that ultimately occurs. This in no way invalidates the conclusion that hypophysectomy alters the response to pancreatectomy since, as we shall see, the most

TABLE 1

The survival and excretion during fasting of glucose, nitrogen and acetone by various cats

TYPE OF ANIMAL	NUMBER		SURVIVAL	URINE				BLOOD SUGAR
				Glucose	Nitrogen	Acetone	D/N	
			days	*g/k/d**	*g/k/d**	*mgm./k/d**		*mgm./100 cc.*
Depancreatized	22	Average	5.3	3.2	1.3	116	2.7	347
		Range	2–12	1.6–6.4	0.8–2.2	28–275		212–788
Hypophysectomized-depancreatized	19	Average	22.0	0.4	0.7	5	0.6	190
		Range	8–85	0.0–1.5	0.3–0.9	0–27		16–355
Adrenalectomized-depancreatized	18	Average	14.0	0.6	0.6	13	1.0	186
		Range	5–28	0.0–1.6	0.3–0.9	3–48		13–362

* Signifies grams or milligrams a kilogram a day.

striking changes are observed in well-nourished animals immediately after excision of the pancreas.

(*b*) *Glycosuria and blood sugar level.* Since one of the most interesting features of the depancreatized animal is the persistence of a high degree of glycosuria during fasting, we have made a large number of observations of the glucose excretion during the first three days after pancreatectomy in both normal and hypophysectomized cats. Table 1 and figure 1 show the marked reduction that occurs. In fact, it is not unusual to find that by the third day the hypophysectomized-depancreatized cat has ceased to excrete glucose and at no time does the excretion in any way approach that of the depancreatized animals. It has already been mentioned that fasting reduces the blood sugar of hypophysectomized cats to dangerous levels and it is a remarkable fact that even total removal of the pancreas may not protect the fasting hypophysectomized animal from death due to hypoglycemia. For this reason and also for the fact that the depancreatized cat usually develops renal failure after the third day, we have not con-

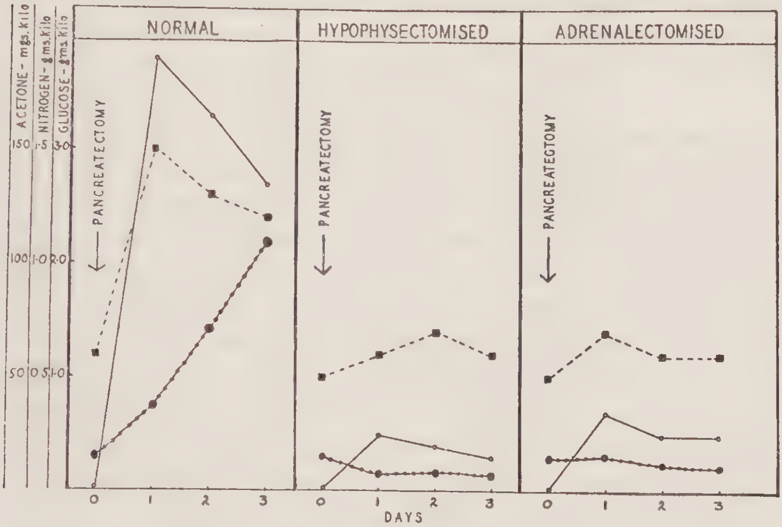

Fig. 1. The effect of total pancreatectomy upon the urine glucose ○——○, urine nitrogen ■------■ and urine acetone ●-•-•-•-● excretion of fasting normal, hypophysectomized and adrenalectomized cats. The curves are constructed upon data from 22 normal, 19 hypophysectomized, and 18 adrenalectomized cats.

tinued our observations beyond this point. Since the urine glucose of a depancreatized animal more or less reflects the level of the blood glucose, it is not surprising in view of the urinary alterations in the doubly-operated animals to find that the blood sugar is reduced on the average to about the level at which glycosuria ceases. These average values do not however reflect the extraordinary fluctuations in blood sugar that are encountered in these animals, since in the course of a few days they may fall from levels observed in the depancreatized cats to those usually encountered in animals suffering from hypoglycemic shock.

(*c*) *Nitrogen excretion.* As table 1 and figure 1 indicate, the decreased glycosuria during fasting is accompanied by a corresponding fall in nitrogen excretion. If this is interpreted in the usual sense, it implies a marked degree of protein sparing as a result of hypophysectomy. This might be due either to an increased glucose utilization or else to a decrease in the breakdown of the tissue protein. If it is due to the latter, then it would be expected that the glycosuria would be correspondingly decreased while the former indicates a capacity of the tissues to utilize glucose that is quite at variance with the view that in the absence of insulin the oxidation of this substance is almost entirely suppressed. Further reference will be made to these alternatives later.

(*d*) *Ketonuria and acidosis.* The extensive ketonuria which is such a common feature of diabetic acidosis and coma in man, is not encountered in the depancreatized cat and dog. Nevertheless, the impending onset of acidosis and coma in the cat is heralded by the early appearance in the urine of increased quantities of the so-called acetone bodies. These steadily increase in amount and contribute in some part to the characteristic acidosis that in the cat usually develops about the fourth or fifth day. In table 1 and figure 1 are recorded one of the most important alterations in pancreatic diabetes that is brought about by the removal of the hypophysis. It will be observed that ketonuria does not develop; in fact, the quantities of acetone bodies encountered under these conditions are no greater than those observed in ordinary cats fasted for similar periods. Since the extent of the ketonuria more or less reflects the severity of the acidosis, it is not altogether surprising to find that the hypophysectomized-depancreatized animal does not develop acidosis. In fact, it is probable that it is this immunity from acidosis that more than any other factor contributes to their extended survival since gross glycosuria in itself is not, so far as we know, an obstacle to continued existence provided that the caloric loss is met by an increased food intake. The cause of death of over 90 per cent of our depancreatized cats has been acidosis, but not one of the doubly-operated animals has succumbed to this complication, unless it was an occasional animal in which autopsy has disclosed a large remnant of the pituitary. As already mentioned, these animals either die at an early date from hypoglycemia or succumb after a long survival to the effects of this complication plus those of inanition.

(*e*) *The D/N ratio.* In the past much emphasis has been placed upon the dextrose-nitrogen ratio in the urine of a fasting depancreatized animal as an indication of the fact that under these circumstances, since glucose is not utilized by the tissues, a constant proportion of the tissue (or dietary) protein is convertible into glucose. While the validity of a high and constant D/N ratio in total or phloridzin diabetes as an indicator of the vertical suppression of glucose oxidation has been the subject of marked difference of opinion, it cannot be denied that this ratio reaches a more or less constant value after pancreatectomy. Since the removal of the pituitary not only decreases the nitrogen excretion but may also cause a disappearance of glucose from the urine, the exact value of the D/N ratio becomes of little interest since its interpretation under these conditions requires the same modifications as does the earlier view that glucose utilization is next to impossible in the absence of the pancreas. Table 1, however, shows that there is on the average a disproportionate decrease in the glucose and nitrogen excretion, in consequence of which the D/N ratio is greatly reduced.

How does hypophysectomy ameliorate a pancreatic diabetes?

While all investigators are agreed that in several species hypophysectomy modifies a pancreatic diabetes, there is as yet no complete agreement of the manner in which these alterations are brought about. There are, however, several possibilities, some of which have been explored.

(1) It is the removal of the anterior lobe of the pituitary that is responsible for the effects observed. This was first demonstrated by Houssay and Biasotti (6) in the toad. Lukens and I have also noted in several cats that the accidental retention of the posterior lobe did not allow a pancreatic diabetes to develop in its usual manner. These findings are in keeping with those of Pencharz, Cori and Russell (7) who have adequately shown that retention of the posterior lobe did not alter the usual sensitivity of the totally hypophysectomized rat to insulin, while conversely the excision of the posterior lobe was not followed by development of insulin sensitivity.

(2) The marked reduction in fasting glycosuria and nitrogen excretion as well as the absence of ketonuria might be explained if it could be demonstrated that the hypophysectomized-depancreatized animal had resumed the oxidation of glucose in sufficient quantity to spare the protein and fat stores of the body. There is some evidence that this is so since Houssay and Biasotti (8), and Biasotti (9) have reported that the R.Q. may rise to a considerable degree in some hypophysectomized-depancreatized animals. In others, however, but little change was found. A better criterion for an increase of glucose oxidation is the study of the R.Q. of the isolated tissues of these animals. Schorr, Richardson and Sweet (10) found that in a non-nutrient medium the R.Q. of skeletal muscle was higher in the hypophysectomized-depancreatized dog than in the depancreatized dog. Fazekas, Campbell and Himwich (11), however, have found that the isolated renal tissue of hypophysectomized-depancreatized dogs cannot oxidize glucose. The presence of a high or low blood sugar level at the time of the observation did not affect the results.

The study of the glucose tolerance curve of these animals has also yielded conflicting results. Houssay and Biasotti (8), and Biasotti (9) found that the removal of injected glucose was more rapid in their doubly-operated animals than in those depancreatized, but was not as rapid as in the normals. Soskin, Mirsky, Zimmermann and Heller (12) found that in dogs with high initial blood sugar levels (300 to 400 mgms. per cent), injected glucose raised the blood sugar to very high levels (600 mgm. per cent) but it returned to the *initial* level in about the same time that it returned to this point in normal animals. On the other hand, when the initial blood sugar was at the normal level (100 mgm. per cent), there was a marked delay in its return to the starting point. Barnes and Regan (13) have reported on one dog in which the ingestion of 100 grams of glucose was not followed by glycosuria, but the intravenous administration of glucose was followed by markedly abnormal blood sugar levels.

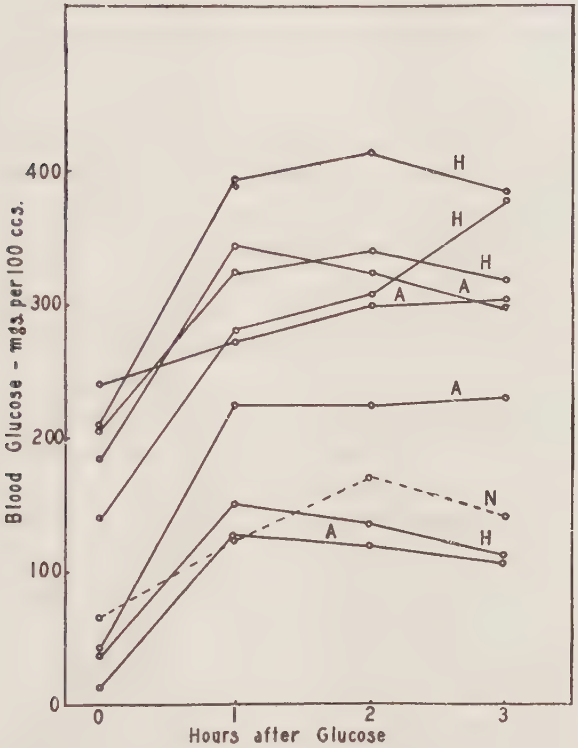

FIG. 2. Blood sugar curves following the intraperitoneal injection of 1 gram of glucose per kilogram into hypophysectomized-depancreatized cats (*H*), adrenalectomized-depancreatized cats (*A*), and a normal cat (*N*).

Our own experiences have been equally inconclusive (figure 2). In general, we have found that hypophysectomized-depancreatized cats with high initial blood sugar levels had markedly abnormal glucose tolerance curves although they were not as "diabetic" as those of ordinary depancreatized cats. On the other hand, the administration of often considerable amounts of glucose to animals with low initial blood sugar levels or to those in hypoglycemic shock frequently was followed by almost normal curves and little, if any, of the glucose was excreted. Furthermore, the addition of glucose (6 grams a day) to the diet of "healthy" hypophysectomized cats led to a practically quantitative excretion of the extra glucose. Quite recently Reid (14) has reported that as judged by the continuous infusion technique, the tolerance of hypophysectomized-depancreatized cats to glucose is even less than that of the depancreatized animal.

Our present conclusion is that although the capacity of the hypophysectomized-depancreatized animal to oxidize glucose is on occasion somewhat greater than that of the depancreatized animals, other factors must be looked for to account for the alterations that are observed in metabolism.

(3) An alternative explanation first advanced by Houssay and Biasotti (8) to account for the diminished glycosuria and nitrogen excretion of fasting hypophysectomized-depancreatized animals is that the formation of glucose from the non-carbohydrate reserves of the body (protein or perhaps fatty acids) is greatly diminished by the absence of the hypophysis. It is well recognized that during fasting the blood sugar level and minimal tissue requirements of glucose are met by the conversion of a certain proportion of the tissue proteins into glucose (45 to 60 per cent). Following pancreatectomy the loss of glucose in the urine compels the fasting organism to accelerate these processes, in consequence of which the nitrogen excretion is also increased. The exact manner in which the body protein and fat stores are mobilized to meet the caloric demands imposed by fasting are not clearly understood, but there is reason to believe that the hypophyseal hormones exert a marked stimulating action on these processes. Since the withdrawal of insulin from the body undoubtedly slows down the rate of carbohydrate oxidation, it is not illogical to suppose that there also exist other hormones whose withdrawal would greatly reduce the rate at which glucose was made available to the organism. Since the major part of the deamination of amino acids and the catabolism of fatty acids takes place in the liver, it may be expected that the hypophyseal hormones either directly or indirectly exert their major influence

upon this organ. In support of this view are the findings of Campos, Curutchet and Lanari (15) that hypophyseal implants are unable to raise the blood sugar of hepatectomized toads, while Houssay and Foglia (16) have reported that the hyperglycemia produced by anterior pituitary extracts in dogs rapidly disappears after removal of the liver. In addition, Fluch, Greiner and Loewi (17) found that the perfused livers of hypophysectomized frogs are unable to liberate glucose at the same rate as those of normal animals.

To my mind, it is probable that both of the possibilities discussed are operative in reducing the glycosuria of fasted hypophysectomized-depancreatized animals. The available evidence would indicate that there is some restoration of the ability of the tissues to oxidize glucose, while at the same time the amounts presented to them are reduced to a level which is within their capacity to dispose of without excessive urinary loss.

If this explanation of the effect of hypophysectomy upon pancreatic diabetes is correct, then it must be concluded that the hypophyseal hormone or hormones influencing carbohydrate metabolism also have a dual function. One effect of their injection would be to accelerate the catabolism of protein and fat and thus increase glucose formation in the liver, while at the same time, by their peripheral action, they decrease the rate of carbohydrate oxidation and thus directly antagonize the peripheral action of insulin. It is therefore of some importance that Marks (18) has recently found that in the decapitated-liverless (eviscerated) cat, certain anterior pituitary fractions, notably the lactogenic fraction, prevent the deposition of muscle glycogen and bring about a diminution of the fall in blood sugar that usually follows the infusion of glucose and insulin into these preparations.

(4) We have dealt thus far with the effects of hypophysectomy upon pancreatic diabetes as though the hypophyseal hormones acted directly upon the liver and tissues. However, it must be recalled that removal of the hypophysis is followed by atrophy and hypofunction of a number of endocrine organs, included among which are some whose secretions are known to influence carbohydrate metabolism. Furthermore, the trophic nature of many of the hypophyseal hormones suggested to us the possibility that the influence of this organ upon metabolism might be mediated by some other endocrine

gland. We have therefore examined the effect of excision of certain other endocrine glands upon pancreatic diabetes. Some of these were shown not to have any effect. These are: (a) *The thymus.* Table 2 shows quite distinctly that removal of this organ does not prolong the life-span nor alter the character of the diabetes of totally depancreatized cats. (b) *The thyroid.* Excision of the thyroid has been found to decrease the glycosuria and reduce the insulin requirement of human diabetics (19). In the depancreatized dog, Houssay and Biasotti (8) found that thyroidectomy did not alter in any way the usual consequences of pancreatectomy, a result which we have confirmed in the cat (table 2).

TABLE 2

The effect of a previous thymectomy or thyroidectomy upon pancreatic diabetes

TYPE OF ANIMAL	NUMBER OF ANIMALS	SURVIVAL	URINE		
			Glucose	Nitrogen	D/N
		days	*g/k/d**	*g/k/d**	
Depancreatized cats	22	5.3	3.2	1.3	2.5
Thymectomized-depancreatized cats	3	5.3	3.0	1.3	2.3
Thyroidectomized-depancreatized cats	5	7.6	2.7	1.1	2.5
Thyroidectomized-depancreatized dogs (Houssay)	5	14.0	2.5	1.1	2.3

* Signifies grams per kilogram per day. Values for first three days after pancreatectomy and fasting.

The other endocrine glands, one of whose secretions is known to affect carbohydrate metabolism, are the adrenals, and since we have demonstrated that excision of these organs exerts a striking effect upon pancreatic diabetes, our experiments will now be considered.

The effect of total adrenalectomy on pancreatic diabetes

The discovery by Blum in 1901 (20) that the hormone of the adrenal medulla—epinephrine or adrenaline—causes glycosuria in normal animals stimulated attempts to excise both the pancreas and adrenals from cats and dogs. These experiments were based on the hypothesis that the uncompensated activity of the adrenal medulla following pancreatectomy might be a contributory factor in the development of the glycosuria that follows this operation. Until recently all these earlier experiments (which have been reviewed elsewhere (5)) were invalidated by the poor condition and short survival of the animals after the removal of both these endocrine glands. In our work we have been more successful, largely owing to the advantage of having at our command potent extracts of the adrenal cortex. By the use of these extracts we have been able to keep totally depancreatized and adrenalectomized cats alive for several weeks.

The removal of these organs is best accomplished in stages either (a) by first removing both adrenals and then at a later date the pancreas, or (b) by first removing one adrenal and then at the second operation the remaining adrenal and the pancreas. These methods have recently been employed by Long, Lukens and Dohan (21) to demonstrate similar effects in dogs.

More recently, in association with Dr. K. W. Thompson and Miss E. G. Fry, I have found a much easier way of demonstrating the effects of adrenalectomy upon a pancreatic diabetes. This is to perform partial pancreatectomy on rats in the manner described by Pincus and Shapiro (22). The operation is best done soon after weaning, and on attaining an age of about 50 to 60 days, many of these animals are found to be excreting glucose, often in quantities of two to three grams a day. In spite of this high level of glycosuria, the animals grow normally and remain in excellent health. There are distinct advantages to the use of such preparations in the study of experimental diabetes for even if no glucose is being excreted, it will usually be found that the injection of a suitable pituitary extract rapidly causes its appearance in the urine.

The results we have obtained with these two types of preparations may now be considered:

(*a*) *Totally adrenalectomized-depancreatized cats.* Reference to table 1 shows that the survival of totally adrenalectomized-depancreatized cats is extended beyond that ordinarily found in those simply depancreatized, but in no instance were such long survivals encountered as those observed in hypophysectomized-depancreatized cats. The reasons for this finding are two in number: (a) All the animals received cortical extract, but in many of them insufficient amounts were administered. Furthermore, the large quantities required to maintain these animals constituted an expense that has necessitated a limitation of many experiments. (b) It is now realized that the diet of pancreas and canned salmon that was fed to these animals is probably the least suitable for them on account of its high potassium content (23). Nevertheless, there is no doubt that in the present series of animals the average survival was nearly three times as long as that of the depancreatized cats.

Even this extended survival would be of minor interest were it not for the fact (table 1) that the same alterations are observed in the urinary glucose nitrogen and acetone body excretion as were previously found in the hypophysectomized-depancreatized cats. There is the same failure of the glucose and nitrogen excretion to rise to high levels after pancreatectomy (fig. 1) while, as before, the characteristic ketonuria with accompanying acidosis does not develop. When it is also seen that the blood sugar level undergoes the same wide fluctuations, it is difficult to avoid the conclusion that hypophysectomy and adrenalectomy produce an amelioration of a total pan-

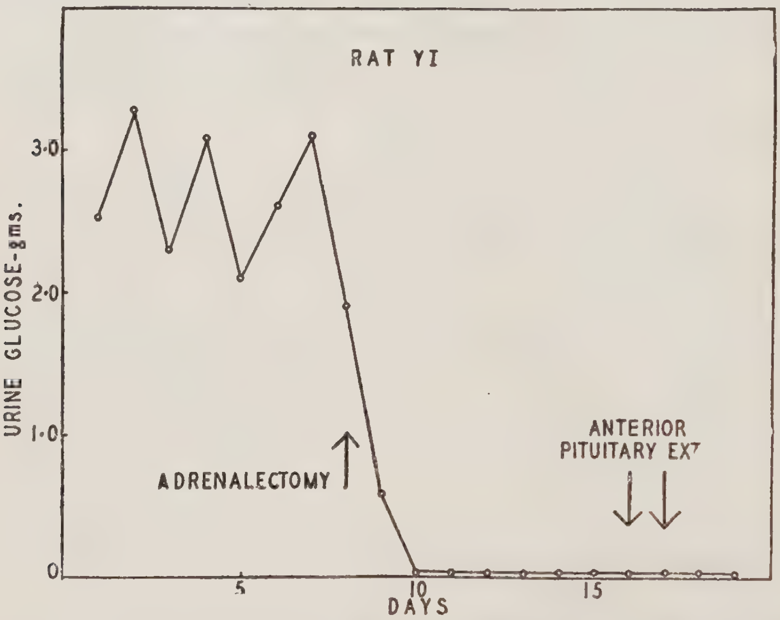

FIG. 3. The effect of total adrenalectomy upon the spontaneous glycosuria of a partially depancreatized rat (weight 352 grams). Note that after adrenalectomy the injection of a potent saline extract of fresh beef anterior pituitary does not cause a return of the glycosuria. The food intake was constant throughout.

creatic diabetes of the same degree and probably by interference with similar processes. It is of great interest to us that Houssay and Biasotti (24) have recently reported that total adrenalectomy modifies pancreatic diabetes in the toad to a degree comparable to that obtained by hypophysectomy.

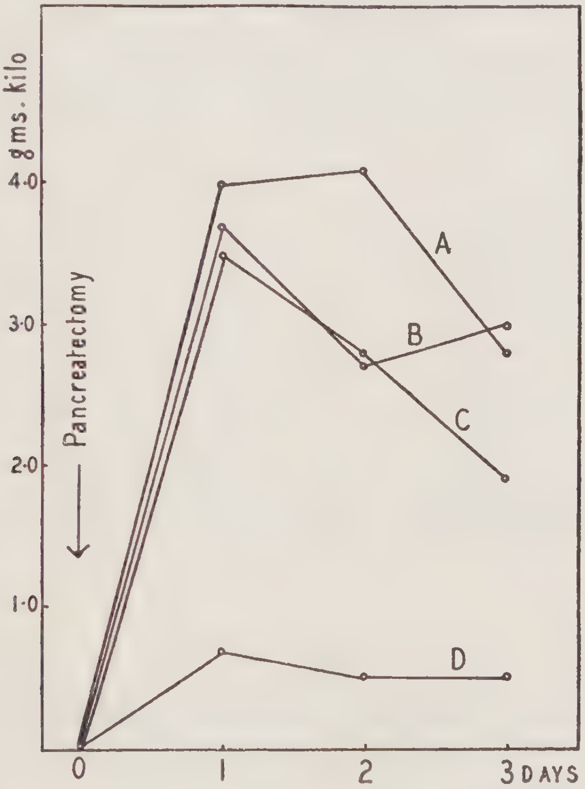

Fig. 4. Glycosuria (grams/kgm./day) following total pancreatectomy in (*A*) 12 cats with intact adrenals, (*B*) 6 cats with the adrenals denervated, (*C*) 5 cats with the adrenal medullae removed, (*D*) 18 cats with both adrenals removed. All the animals were in the fasting condition.

The glucose tolerance curves indicate that there is but little improvement in the capacity of the tissues to utilize glucose but like the hypophysectomized-depancreatized cats, an occasional animal may tolerate glucose without marked glycosuria, especially if the initial blood sugar is at a low level (fig. 2).

(*b*) *Adrenalectomized-partially depancreatized rats.* For the study of the effects of total adrenalectomy on a partial pancreatic diabetes, we have used partially depancreatized rats ingesting a constant amount of food and excreting considerable quantities of glucose daily. In these animals total adrenalectomy promptly causes a disappearance of glycosuria (fig. 3). Such animals remain in excellent condition for long periods after adrenalectomy provided they are given salt in their drinking water, and since the glycosuria does not ultimately reappear, its disappearance cannot be attributed to acute adrenal insufficiency.

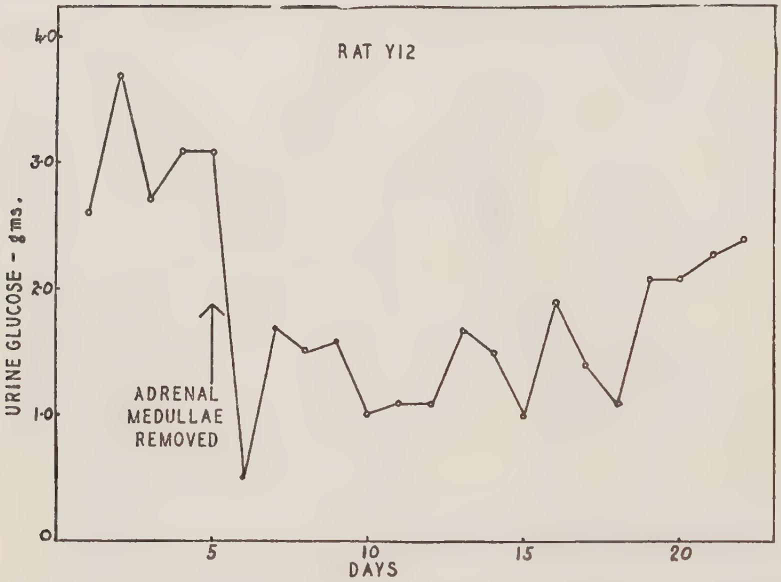

FIG. 5. The effect of removal of all adrenal medullary tissue upon the spontaneous glycosuria of a partially depancreatized rat (weight 262 grams). Note that after an initial decrease the glycosuria returns to approximately its initial level. The food intake was constant throughout.

The effects of removal of the adrenal medulla upon pancreatic diabetes

Since the adrenal gland is composed of two distinct endocrine organs, it is necessary to determine which of these it is whose removal brings about an amelioration of pancreatic diabetes. The experiments we have conducted on this point are quite decisive and indicate that it is the loss of the cortical portion of the gland that is the determining factor. These are:

(a) Depancreatized cats with denervated or demedullated adrenals rapidly succumb to the effects of pancreatectomy. They excrete quantities of glucose, nitrogen and acetone bodies that are almost identical with those found in operated animals with intact adrenals (fig. 4).

(b) Evans (25) has shown it is possible completely to remove the adrenal medullae from rats. The remaining cortical cells rapidly regenerate so that in ten to eighteen days the glands have been reconstituted but, of course, no longer possess a medulla. If this operation is performed upon a partially depancreatized rat, it is found (fig. 5) that after an initial decline the glycosuria steadily returns to its initial quantity. If total adrenalectomy is now performed, the glycosuria disappears and does not return.

It may therefore be concluded, as others have done (26), that removal of epinephrine from the body does not influence either a total or partially pancreatic diabetes and consequently attempts to improve human diabetes by adrenal denervation are not likely to succeed unless severe injury is inflicted upon the cortex by interference with its blood supply. Rogoff (27) has already called attention to one such attempt that was followed by the development of a fatal adrenal insufficiency.

How may loss of the adrenal cortex modify pancreatic diabetes?

The modifications that removal of cortical tissue brings about in pancreatic diabetes may be due to a direct participation of its hormones in the processes of metabolism or else may be merely secondary to unrelated changes in other bodily functions that are produced by the excision of this organ.

To consider the latter possibility first: The alterations in the fluid and salt balance that follow adrenalectomy may be so profound that the normal mechanisms by which glucose is formed in the liver become impaired. Such a condition would find an analogy in the disappearance of glycosuria in a depancreatized dog in which hepatic insufficiency had developed as a result of fatty infiltration following the administration of a choline-free diet (Best and Hershey (28)). We cannot, however, agree that this is the explanation of our findings since all our animals except the rats received cortical extracts. Our reasons are as follows:

(a) As figure 1 shows, the effects of adrenalectomy upon diabetes in the cat are well marked during the first forty-eight hours after pancreatectomy. Since the full effects of adrenal insufficiency are not manifest for several days, it is considered unlikely that any loss of the water and salt hormone of the cortex would be reflected upon carbohydrate metabolism at such an early date.

(b) While it is true that some of our earlier animals received inadequate amounts of cortical extract, this would appear not to have been the case in those animals which were first adrenalectomized and maintained on extract for as long as four weeks before pancreatectomy. Following this last operation, the maintenance dose of extract was increased threefold without any exacerbation of the diabetes. It is of course possible that the optimal level of dosage for the appearance of a full diabetes has not yet been tried.

Verzar and his co-workers (29) have found that removal of the adrenal cortex markedly interferes with the phosphorylation processes by which fats and carbohydrates are transferred through the intestinal wall. Since chemical changes involving the formation and breakdown of phosphorus compounds are of fundamental importance in the metabolism of carbohydrates in the tissues, the possibility that disturbance of these mechanisms would alter the response to pancreatectomy is worthy of further investigation. At present, however, we have no evidence to support this hypothesis.

Finally, there is one explanation of the similarity of the effects of adrenalectomy and hypophysectomy upon diabetes that implies that one or all of the hypophyseal hormones exert their effects upon metabolism by stimulation of the adrenal cortex. If this were a trophic action resulting in the liberation of some principle from the adrenal, then it would be expected that just as thyroidectomy abolishes the effect of the thyrotropic hormone, adrenalectomy would render ineffective any influence of the hypophyseal hormones upon metabolic processes. This hypothesis we have tested by comparing the effects of different pituitary extracts and other substances upon the glycosuria and ketonuria of partially depancreatized and normal rats in which either the adrenal medullae or both adrenals had been removed. Before reviewing these results, let us consider the effects of the injection of anterior pituitary extracts in normal animals.

The "diabetogenic" action of anterior pituitary extracts

Soon after Houssay's announcement that hypophysectomy altered the character of pancreatic diabetes, it was reported almost simultaneously by Houssay, Biasotti and Rietti (30), E. I. Evans (31), and Barnes and Regan (13) that the continued injection of crude alkaline or acid extracts of the anterior pituitary caused glycosuria and hyperglycemia in normal dogs.[2] This effect presents certain peculiarities: (a) It is only observed in fed animals, particularly those on a high-carbohydrate diet. (b) It requires treatment for two or three days before the effect develops. (c) Large quantities of extract are required. Houssay gives the equivalent of 1.5 to 2.0 grams of fresh anterior lobe per kilogram daily. (d) After the glycosuria has persisted for several days, it disappears in spite of continued injections (E. I. Evans, (31); Shipner and Soskin, (32); Young, (33)). (e) It is claimed that at the time glycosuria is present, the liver glycogen is increased (Houssay and Foglia, (16)). (f) The degree of glycosuria is much greater than the increase in blood sugar would appear to warrant (cf. Houssay, Biasotti and Rietti, (30)). (g) At the height of its action the injected animals exhibit a decreased glucose tolerance and a failure of the respiratory quotient to rise after such glucose ingestion (Biasotti (35)). (h) There develops marked insulin resistance (Di Benedetto (36)) and an exaggerated response to the hyperglycemia action of epinephrine (Houssay and Di Benedetto (37)). (i) There is an increased excretion of acetone bodies (Rietti (38)).

The main effect of these extracts is the production of a condition that is almost indistinguishable from that produced by insulin deficiency, although the injected animals have, of course, retained an intact pancreas. The importance of this observation in relation to clinical diabetes can scarcely be overemphasized since it furnishes the first evidence that many, if not all, of the features of the diabetic state can be produced by an extra-pancreatic agency. In fact, E. I. Evans (31) has reported that in two of his animals severe diabetic acidosis and coma resulted from the injections, a report that so far has not been confirmed.

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[2] In 1927, Johns, O'Mulvenny, Potts and Laughton (34) describe a "protein free" extract of the anterior pituitary that caused mild glycosuria in dogs.

In partially depancreatized animals, the effects of these extracts are much exaggerated and animals that were without glycosuria before the injection soon excrete large quantities of glucose.

The most sensitive preparations to the action of these extracts are animals deprived of all the pancreas and the pituitary. These furnish admirable test objects for this "diabetogenic" action inasmuch as even when fasting and sugar-free, the administration of relatively small amounts of anterior pituitary extract (0.3 to 0.5 gram fresh anterior lobe per kilogram in doubly-operated cats) rapidly causes the appearance of a considerable degree of glycosuria and ketonuria. In fact, great care must be exercised in administering extracts to these animals, as diabetic acidosis and coma are readily induced. We have had several otherwise healthy hypophysectomized-depancreatized cats die of this condition within forty-eight hours after the initial injection. Inasmuch as these extracts exert their effects in the absence of the pancreas, a direct neutralization of insulin is not the manner by which they are produced.

Since both glycosuria and ketonuria are caused by these crude anterior pituitary extracts, some workers have stated that more than one principle is involved in this "diabetogenic" action. In fact, it has become customary to speak of the glycosuric and ketogenic hormones of the anterior pituitary, a circumstance that is not warranted at present since it is quite possible that the increased blood and urine acetone body content might merely be secondary to a disturbance in carbohydrate metabolism. Thus, although the normal fasting rat develops a ketonuria without glycosuria following anterior pituitary injection, yet the partially depancreatized rat develops marked glycosuria (fig. 6) without ketonuria when injected with the same extract, a difference that might be dependent upon the quantity of carbohydrate undergoing metabolism. Anselmino and Hoffman (39), however, claim to have separated by ultrafiltration at different hydrogen ion concentration two principles, one of which increases the blood acetone content and the other causes a fall in liver glycogen.

Whether the last factor is identical with that producing glycosuria remains conjectural.

The injection of crude saline or alkaline extracts of the anterior pituitary does not produce glycosuria in fasting normal rats, and it is only with difficulty that this effect can be shown in fed animals. On the other hand, ketonuria is markedly increased in fasting normal animals and in those on a high-fat diet (Burn and Ling (40); Black, Collip and Thomson (41)).

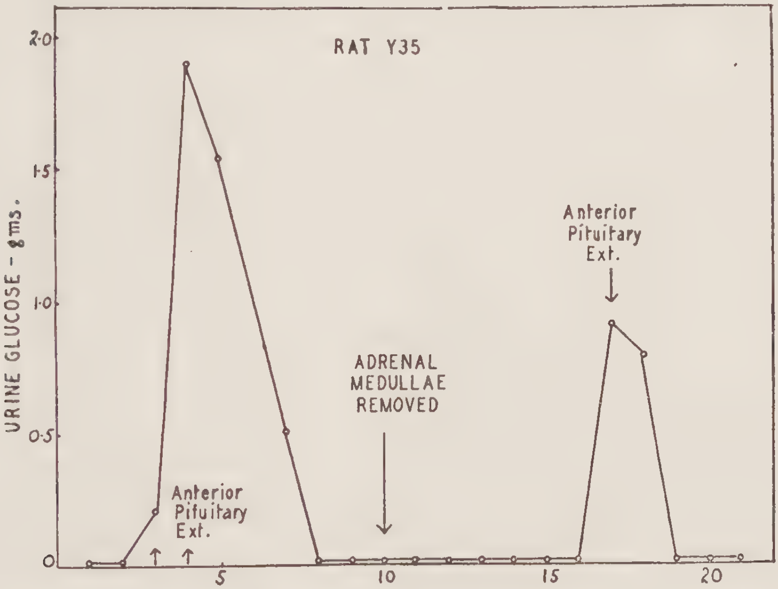

FIG. 6. Showing that removal of all adrenal medullary tissue from a partially depancreatized rat (weight 146 grams) does not prevent the glycosuric action of a saline extract of fresh beef anterior pituitary. The food intake was constant throughout.

Glycosuria is, however, readily produced in the well-fed, partially depancreatized rat, or if it is already present, is greatly exaggerated. Of greater importance from the present argument is the finding that removal of the adrenal medullary tissue does not alter this response (fig. 6). In similar types of experiments conducted upon the increased ketonuria that follows the injection of anterior pituitary extracts into fasting rats, Fry (42) has been able to show that loss of the adrenal medulla does not prevent this ketonuria (fig. 7). These findings would appear to firmly establish the conclusion, already arrived at by a study of the effects of the removal of epinephrine from the body upon a total diabetes, that in the genesis of the diabetes provoked by excision of the pancreas or by anterior pituitary extracts, epinephrine does not play any decisive rôle. This conclusion is further supported by the findings of Houssay, Biasotti and Rietti (43) that demedullation of the adrenals in normal dogs does not inhibit the "diabetogenic" action of the anterior pituitary extract that they used.

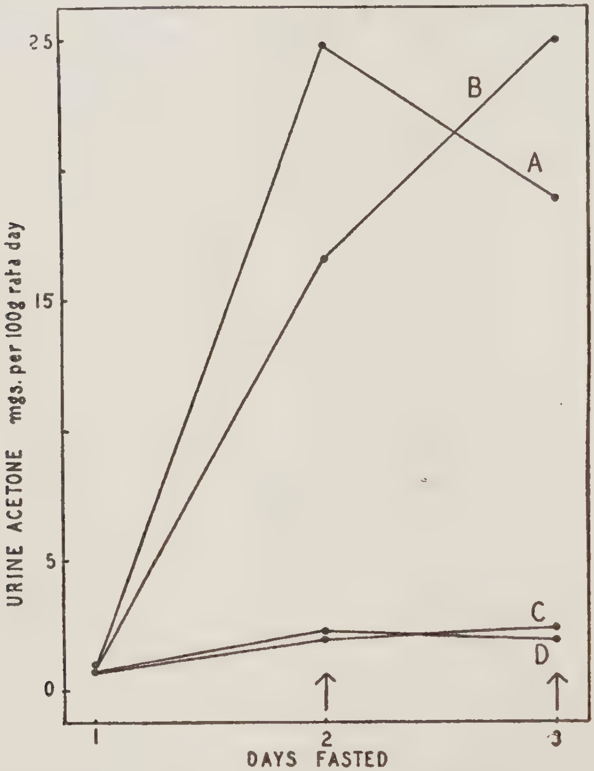

Fig. 7. The effect of an alkaline extract of anterior pituitary upon the acetonuria of (*A*) normal rats, (*B*) rats with demedullated adrenals, (*C*) adrenalectomized rats maintained with NaCl, (*D*) adrenalectomized rats maintained with cortical extract (Upjohn). The anterior pituitary extract was injected on the second and third day of fasting. (From the data of Fry (42).)

The repetition of similar experiments in rats with both adrenals removed would appear to establish conclusively that in this species the loss of the cortical tissue entirely prevents both the glycosuric and ketogenic action of the anterior pituitary. In figure 8 is recorded the response of a partially-depancreatized rat to a saline extract of the anterior pituitary before and after removal of the adrenals. It will be observed that a marked glycosuria developed on two occasions when this extract was administered before removal of the adrenals, but that the same extract was quite without effect one week after their excision. These results cannot be accounted for by the poor condition of the animal after adrenalectomy since at the present time (50 days after operation) the rat is still alive and well upon a high NaCl regime with occasional injections of cortical extract. Another injection of anterior pituitary twenty-two days after operation also failed to cause glycosuria. Another example of the effect of total

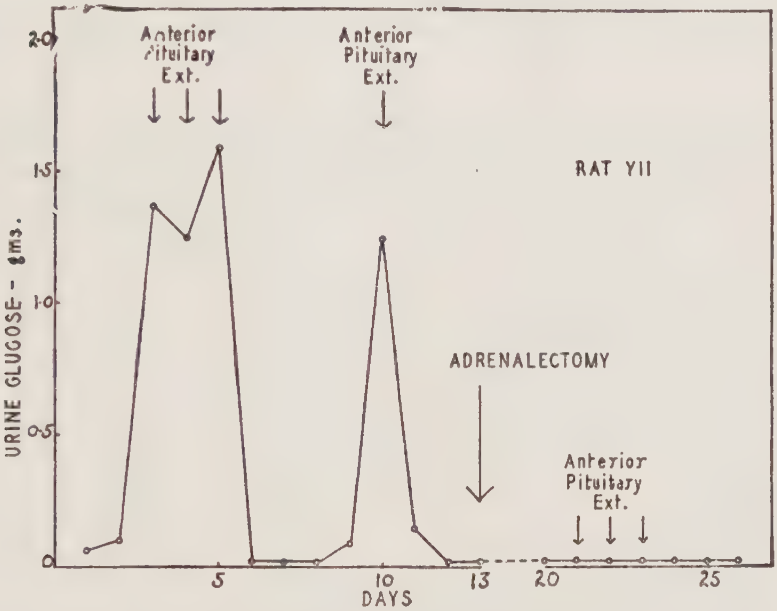

Fig. 8. The effect of total adrenalectomy upon the glycosuric action of a saline extract of fresh beef anterior pituitary in a partially depancreatized rat (weight 224 grams). The food intake was constant throughout.

adrenalectomy is seen in figure 3 where a rat in which a previous high level of glycosuria was abolished by adrenalectomy also failed to respond to a subsequent course of anterior pituitary injection.

Fry (42) has found that in contrast to adrenal demedullation, total adrenalectomy abolishes the ketogenic action of anterior pituitary in fasted rats (fig. 7), a result that has been confirmed by MacKay and Barnes (44).

Certain anterior pituitary extracts increase the liver fat of fasting rats (Best and Campbell (45); Anselmino and Hoffmann (46)). This fatty infiltration is also prevented by removal of the adrenals (Fry (42); MacKay and Barnes (47)).

TABLE 3

The effect of various pituitary fractions and other substances on the glycosuria and acetonuria of hypophysectomized-depancreatized and adrenalectomized-depancreatized cats

EXTRACT USED	TYPE OF ANIMAL*	NUMBER OF EXPERIMENTS	INCREASED GLYCOSURIA	INCREASED KETONURIA
Thyrotropic (Collip)	H.D.	2	0	0
Growth (Collip)	H.D.	2	2	0
Prolactin-adrenotropic (Collip)	H.D.	4	4	0
Prolactin-adrenotropic (Collip)	A.D.	6	0	0
Prolactin-adrenotropic (Collip) (boiled)	H.D.	7	7	0
Boiled prolactin (Riddle)	H.D.	3	3	0
Boiled prolactin (Riddle)	A.D.	3	0	0
Pituitrin P.D.	H.D.	1	0	0
Adrenaline P.D.	H.D.	7	6	1
Adrenaline P.D.	A.D.	6	3	0
Cortical extract (Upjohn)	H.D.	2	0	0
Ascorbic acid	H.D.	1	0	0

* H.D. signifies hypophysectomized-depancreatized.
A.D. signifies adrenalectomized-depancreatized.

It would therefore seem to be conclusively established that in the rat, at least, removal of the adrenal cortex prevents both the glycosuric and ketogenic action of the anterior pituitary. This conclusion, however, differs from that of Houssay and Leloir (48). These workers state that in the normal dog removal of the adrenals does not reduce a hyperglycemia that had been provoked by anterior pituitary extract. Furthermore, Houssay and Biasotti (24), although admitting that adrenalectomy reduces pancreatic diabetes in the toad, state that implantation of anterior lobe tissue into adrenalectomized-depancreatized animals still causes hyperglycemia. At the present time it is not possible to reconcile these differences of opinion except by invoking the excuse of a species difference. On the other hand, it may be pointed out that our work has revealed large differences in urinary glucose and acetone body excretion while that quoted above is based on small, yet nevertheless significant, alterations in the blood sugar level, none, however, of sufficient magnitude to produce glycosuria with a normal renal threshold.

It is now well recognized that anterior pituitary extracts possess a diversity of action. This is at present interpreted to mean the presence in this gland of several different hormones. Although none of these are as yet available in a pure form, it is of some interest to examine various fractions as to their ability to cause any or all of the different effects that constitute the "diabetogenic" action.

In table 3 are collected our results with different pituitary extracts and other hormones.[3] These were injected into both hypophysectomized-depancreatized cats and also into adrenalectomized-depancreatized cats. It will be seen that the thyrotropic fraction does not increase the glycosuria in the two animals we tested, and the ketonuria was also unaffected. The growth fraction increased the glycosuria but not the ketonuria.

The most interesting results are those obtained with two fractions both rich in the lactogenic principle or prolactin. The first of these was obtained from Professor Collip and designated Al-33. In addition to containing prolactin in considerable quantity, it also possessed adrenotropic activity, and about 0.5 unit of posterior pressor principle per cubic centimeter.[4] This extract produced a marked increase in the glycosuria but not in the ketonuria of a number of hypophysectomized-depancreatized cats. It also produced glycosuria in one hypophysectomized-depancreatized cat in which one adrenal had also been removed and the other adrenal demedullated in the manner described by Houssay and Lewis (26). However, it failed to affect the glycosuria of an equal number of totally adrenalectomized-depancreatized cats (fig. 9). Another finding of some significance is that boiling the extract for five minutes did not destroy its activity in the hypophysectomized-depancreatized cat. It is recognized that treatment of this nature inactivates the diabetogenic action of crude anterior pituitary extracts in normal animals (Houssay, Biasotti and

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[3] We are indebted to Prof. J. B. Collip and the Ayrst McKenna and Harrison Company of Montreal for the various anterior pituitary fractions prepared by Collip's (49) methods. Dr. O. Riddle was also kind enough to send us a sample of prolactin prepared by the method of Riddle, Bates and Dykshorn (50).

[4] Pituitrin P. D. does not increase the glycosuria of hypophysectomized-depancreatized animals (table 3); also, cf. Barnes and Regan (13).

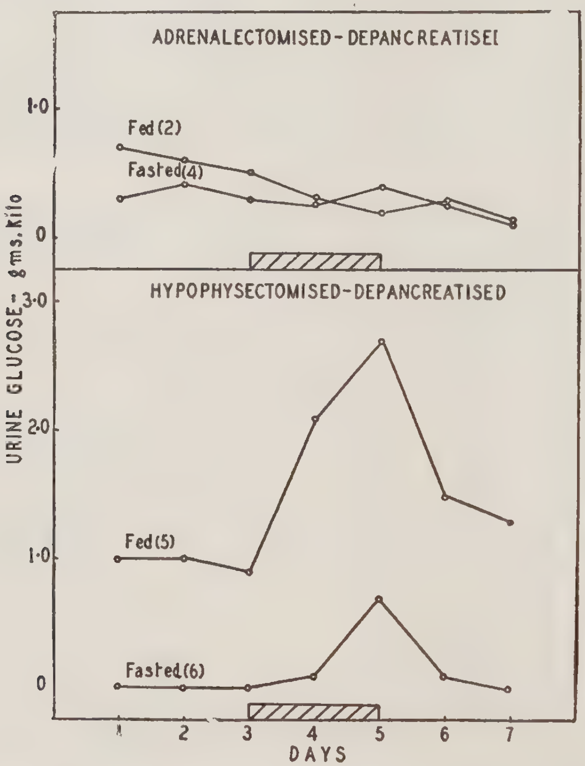

Fig. 9. The effect of an adrenotropic-prolactin fraction (A1-33 Collip) of the anterior pituitary in doses of 10 cc. daily upon the glycosuria of both fed and fasted hypophysectomized-depancreatized and adrenalectomized-depancreatized cats. The number of animals from which these average curves are drawn is given in parenthesis. (From Long and Lukens—unpublished experiments.)

Rietti (43)), but apparently the totally depancreatized and hypophysectomized animal is susceptible to some factor that escapes destruction by this treatment, but which alone is incapable of provoking glycosuria in the presence of the pancreas.

The suggestion that more than one factor is responsible for the production of glycosuria by anterior pituitary extracts in normal animals has already been put forward by Young (33). This investigator comes to the conclusion that three factors operate to produce glycosuria and ketonuria (a) a ketogenic principle that is perhaps identical with the factor causing the increase in liver glycogen (glycogenetic factor); (b) a glycotropic factor that facilitates hepatic glycogenolysis and inhibits the peripheral action of insulin but does not cause hyperglycemia. The absence of this factor in the hypophysectomized animal is held to be responsible for its resistance to the hypoglycemic action of insulin, and also for the fact shown by Cope and Marks (51) that even during insulin hypoglycemia, although epinephrine is liberated, the liver glycogen is not discharged in the usual manner in an attempt to restore the glycemic level. (c) A glycogenolytic factor that directly brings about glycogen breakdown in the liver and which he regards as the factor described by Anselmino and Hoffman (39).

Without prejudice to Young's arguments, and they should be read by all interested in this subject, it would appear simpler at the moment to look upon the diabetogenic activity as composed of (a) heat labile factors, and (b) heat stable factors. In the normal or partially depancreatized animal, the operation of both these principles is necessary to produce glycosuria and ketonuria, the heat-stable factor alone being ineffective. In the totally depancreatized and hypophysectomized animal, the heat-stable factor is able to precipitate glycosuria but not ketonuria without the presence of the heat labile factor. In view of this finding it is of significance that the adrenotropic and lactogenic hormones are the only two pituitary principles known at present that will withstand boiling in water for even limited periods. These two compounds are also both soluble in high concentrations (80 per cent) of alcohol and acetone.

Through the coöperation of Dr. O. Riddle, we were able to obtain a sample of purified prolactin containing two Riddle bird units to the milligram. In quantities of 50 milligrams daily for two days, this preparation either boiled or unboiled produced a striking increase in the glycosuria but not the ketonuria of hypophysectomized depancreatized cats (fig. 10). However, like the adrenotropic-prolactin fraction of Collip, it was inactive in the adrenalectomized-depancreatized cat.

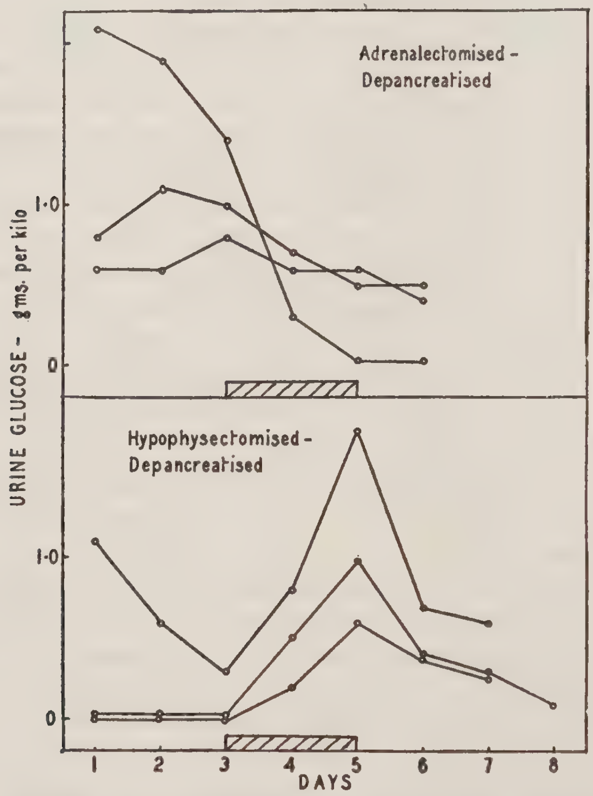

FIG. 10. The effect of prolactin (Riddle 469) on the glycosuria of hypophysectomized-depancreatized and adrenalectomized-depancreatized cats. Fifty milligrams were injected daily for two days. (Long and Lukens—unpublished experiments.)

Now it should be recalled at this point that Marks (18) and Young (52) have reported that both the peripheral action of insulin in the spinal-eviscerated (liverless) cat and the hypoglycemic action of insulin in the normal rabbit are inhibited by the administration of a preparation of prolactin made by the method of Riddle, Bates and Dykshorn (50). These results, together with our own, strongly suggest that one component of the "diabetogenic" action of the anterior pituitary is prolactin or some substance that becomes closely associated with it in the methods at present used in its preparation.

The rôle of the adrenal cortex in the production of glycosuria and ketonuria by the pituitary hormones is by no means clear at the present time. It is also equally difficult to understand why the administration of potent extracts of the cortical hormone concerned with water and salt metabolism fails to restore the glycosuria of adrenalectomized-depancreatized cats to a degree that anterior pituitary extracts do in hypophysectomized-depancreatized animals. It is, of course, possible that this endocrine gland contains an at present unrecognized principle, or else we have gravely underestimated the quantity of the known hormone that is necessary in order for glycosuria and ketonuria to reach the levels encountered in depancreatized animals.[5] I trust, however, that the evidence that I have presented will satisfy you that consideration must be given to the activity of this endocrine organ in any interpretation of the mechanisms by which a normal metabolism is established.

In the present lecture I have largely confined myself to a discussion of such work as I have been personally associated with, and in consequence, have omitted much discussion of the work of others. This has been necessitated by the many papers on the different aspects of the relation of the pituitary and adrenal glands to carbohydrate metabolism. Ultimately, the widely differing views expressed in some of these papers will have to be reconciled, but neither the present time nor occasion seems to me to be suitable for such a task.

Enough, however, has been discussed to demonstrate that the endocrine control of metabolism is far more complex than appeared possible a few years ago. In addition to the many physiological and biochemical problems that await solution, an equally wide field for clinical investigations in the so-called diseases of metabolism is opened before us. Diabetes mellitus is perhaps the one most immediately affected by this new knowledge. In the future, we must cease to focus our interest on the pancreas as the sole determinant in this disorder, but widen it to include extra-pancreatic factors, known and unknown. By doing so, not only may we hope to solve the riddle of its palingenesis, but may also hope to combat more successfully its ravages among our fellow men.

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[5] MacKay and Barnes (53) have found that massive doses of cortical extract (Wilson) increase the ketonuria of fasting female rats.

In preparing a lecture of this nature, the author becomes particularly aware of his indebtedness to those of his colleagues who have assisted him in such experiments as have come from his laboratory. In this respect, I have been fortunate in having as my associates Dr. F. D. W. Lukens, Dr. G. T. Evans and Miss E. G. Fry, of the George S. Cox Institute of the University of Pennsylvania. More recently, this indebtedness must be extended to include Dr. K. W. Thompson of the Laboratory of Physiological Chemistry, Yale University.

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THE METABOLISM OF IRON

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The time at which iron was first used in the treatment of disease is not well fixed. It has been said that in ancient Greece anemia was recognized and treatment consisted in drinking water in which a sword had been allowed to rust. Whether or not this is true it would seem, in the absence of other evidence, that the therapeutic use of iron was in early times, at best, based on empiricism.

Suydenham, in 1661, and Willis, in 1681, described the efficacy of iron therapy in chlorosis (28). In 1746 Menghinis placed the use of iron on a sounder basis by the discovery that this element was a characteristic constituent of the blood and that it was contained "solely in the globular part of the blood." Later Födisch (1832) found the iron content of blood of chlorotics greatly decreased. Ashwell (3) described 15 cases of anemia in adolescent girls and commented on the depraved appetite and insufficient diets of these subjects. In 1842, Andral, Gavaret, and Delafond noted an increase in the number of red blood cells following the medicinal use of iron. Since that time there have been a multitude of investigators who have made studies in this field. It would be impractical to attempt a complete review of this work, and, in view of improvement in methods which have become available in recent years allowing for more accurate work, we shall confine the discussion of the literature largely to the past fifteen year period. Even so, the material presented affords only a representative glimpse of the vast amount of data assembled in the course of the last decade or two. Three phases of iron metabolism have received a great amount of attention: absorption, storage, and utilization. At times it is convenient to consider the subject in the light of such a classification but it must be remembered that often one phase is not independent of the others.

The study of iron absorption has proved to be extremely difficult owing to the multitude of factors which are known or suspected to influence iron following its ingestion. Observations based on the dietary and excretory balance of the metal do not furnish much desired information. The possibility of absorption followed by partial excretion and the possible excretion of iron as a result of incomplete conservation of hemoglobin or other tissue breakdown products are representative of the objections raised to such methods. Further, iron has been shown to be a constant constituent of the bile (52) and it has even been suggested that there is an "entero-hepatic circulation" of iron similar to that of the bile salts (52, 105). If such should be the case, any imperfection in such a cycle of absorption and excretion would only tend to complicate the picture. Under certain conditions the biliary iron secretion may be increased, independently of the food intake.

Some have attempted to follow the rate of absorption by so-called intestinal intubation studies (1). A tube to which are attached two balloons is passed through the duodenum and the balloons inflated by means of their connection to separate lumina of the tube. A third lumen opening between the balloons then offers communication with an isolated portion of the intestine. Known quantities of iron solutions are introduced and, after a definite period, the gut section is washed out. The iron not accounted for is assumed to have been absorbed. The method has been criticized by some who have attempted its use on the grounds that indeterminate quantities of iron in some forms are adsorbed by the mucosa and are thus likely to be attributed to the absorption when such has not occurred.

Experimentally, under anemic conditions with *adequate protein intake*, it would seem that the hemoglobin production in the standardized animal would be the best index we have for determining *the actual amount of iron absorbed* (85), since there is reason to believe that, once in the systemic circulation, the iron is quantitatively utilized *in anemia*. Most clinical studies of anemia have also been based on hemoglobin production, but unfortunately have not in many cases been well controlled. Conclusions concerning the therapeutic value of various iron-containing materials have been hastily and often erroneously drawn from a meagre assortment of data. It should be apparent that one cannot estimate very accurately the effectiveness of orally administered iron by the change in the hemoglobin content of the blood alone. Variations in the circulating fluid volume might very well lead to false interpretations in either direction.

However, contradiction seems to be no prerogative of clinical circles. Experimental results of many workers are in conflict and speculation takes many different courses.

A large number of investigators are firm in the contention that ferrous iron is the only efficacious form for use in anemia (46, 80, 102, 119, 122). Some feel that solubility (72) is all-important. It has even been stated that iron which has formed a part of living tissue is better than clinical preparations (42, 67). On the other hand, Josephs (49), studying nutritional anemia in rats found medicinal iron to be far superior to food iron in causing rapid recovery.

Fifteen years ago in spite of the tendency towards its use clinically, workers were quite convinced that iron was inert in the treatment of anemia (76, 112, 114, 120). Later Robscheit-Robbins and Whipple (86, 116) showed that the efficacy of iron feeding depended on the *actual need* for the element. Short term anemias which do not deplete the animal's iron reserves would not be expected to respond as readily to iron as would the long continued severe anemias where the stores are more depleted and there is a lack of iron. More recently they have shown that iron salts, whether in the ferrous or ferric state, and reduced iron, are utilized with equal facility by the dog in anemia due to hemorrhage. The amount of the metal proved to be the determining factor (85).

Cloetta found forty years ago that the iron in hemoglobin is not absorbed from the intestine in any appreciable quantity (13). This has been corroborated several times since (21, 61, 116, 117). A few years ago, Hill (47) found that α,α di-pyridyl was a reagent specific for ferrous iron, but that hematins gave no reaction with it.

Elvehjem, Hart, and Sherman (23, 24, 98) have attempted to use this method to demonstrate the "availability" of iron in foods. They found that practically all of the iron in its various salts reacted. Iron in liver, muscle, and soy bean was 60 per cent "available," that in wheat 47 per cent, and that in oysters, alfalfa, spinach, and blood about 25 per cent. Hemoglobin regeneration in anemic rats was found to be proportional to the "available" iron as shown by this method. Others do not find results in agreement with these findings (6, 88).

More recently Shackleton and McCance (94) have made a large number of determinations of "ionisable iron" in a wide variety of foods by a modification of the di-pyridyl procedure. They report values which differ somewhat from those of Elvehjem and his associates.

Such studies are probably of limited value because the fact remains that whereas the "availability" of iron salts, such as $FeCl_3$, as shown by the di-pyridyl method is 100 per cent, nevertheless, when given orally to the anemic animal, the salts are poorly utilized. Whipple and Robscheit-Robbins (85) show that in hemorrhagic anemia in dogs, the Fe in the "standard salmon bread ration" is utilized to an extent of about 30 to 40 per cent; that in normal fresh liver, about 45 per cent. Iron salts fed at a level of 40 mgm. (as Fe) per day are utilized to about 35 per cent; and fed at a level of 400 mgm. per day the response in hemoglobin production shows that only from 4 to 7 per cent of the ingested iron is used. On the other hand, colloidal iron (ferric hydroxide) given intravenously, affords a quantitative return of the element as hemoglobin. Thus it would seem that not the form in which Fe is ingested so much as some unknown intraintestinal factor or factors are involved in limiting the absorption and hence the utilization of iron (39).

It has been reported by several investigators (11, 15, 18) that the ingestion of large daily doses of soluble Fe or Al salts is followed by a decrease in blood phosphorous and may result in severe rickets or even death. The simultaneous administration of quantities of NaH_2PO_4 sufficient to unite with the added metals allowed rapid growth and normal bone formation. The mechanism for the first reaction would seem to be the formation of insoluble Fe and P compounds in the intestine, these being excreted at the expense of the body's supply of phosphorous. If this is true, it is logical to suppose that normally something approaching the converse might take place with reference to the absorption of Fe. The average diet often contains over 50 times as much P as Fe.

However, a number of factors may conspire to make absorption of iron difficult regardless of the form in which it is given. The pH of the intestinal tract is probably not so favorable for its unhindered assimilation as heretofore supposed. The work of Robinson (84) and others would indicate a higher pH in the jejunum than is commonly recorded in texts and such a condition would be likely to facilitate the formation of insoluble basic iron compounds. It has been shown from a study of the transformation of iron in pure solution that at a pH above 5.0 a very small concentration of Fe^{++} and still smaller concentration of Fe^{+++} will occur in solution (40).

The rate of dialysis of iron salts across cellophane membranes has been found to be proportional to the amount of salt. The presence of N/10 HCl caused an increased rate while a slight decrease resulted from the presence of N/10 NaOH, and a moderate decrease by the presence of a variety of electolytes including NaH_2PO_4. Marked lowering of the rate existed in the presence of Na_2HPO_4 and Na_3PO_4. These changes occurred in the absence of precipitates (12). Iron combines with a number of amino acids and phosphorous-containing compounds such as nucleic acid to form undissociated compounds (100). Non-diffusible phosphorous compounds (phospholipids and phosphoproteins) form stable complexes with Fe^{+++}, but not with Fe^{++} (109).

Mettier and Minot (71) have shown that the reticulocyte response in hypochromic anemia following oral administration of ferric ammonium citrate in acid-buffered solution is slightly greater than when given in alkali-buffered medium. It has been found by others that the oral administration of this same compound caused no increase in plasma or urinary iron in either normal or anemic individuals, but when the iron was given in acid-buffered medium a slight increase in urinary iron of normals occurred (65). Recently it has been shown that an iron-rich diet has practically no effect on hemoglobin formation during periods of alkalinization, but that after alkalis were discontinued, there was a marked effect comparable to that obtained by adequate therapy with inorganic iron (53).

Gastrectomy apparently causes a decreased response to iron given orally to dogs with chronic experimental anemia (19, 54).

The alkalinity of the pancreatic juice, the relative insolubility of the iron salts of the bile acids, and a host of other conditions are probably inimical to the ready absorption of this element. Whether, indeed, any great amount of iron absorption takes place normally aside from that in the stomach and duodenum is still open to question. At any rate it would seem that the ingestion of foods concomitant with that of iron compounds in the treatment of anemia may be a factor in the assimilation of this element.

If absorption of iron takes place throughout the entire gastro-intestinal tract, then there is a possibility, in the light of some of the above evidence, that Fe^{++} might be more readily absorbed than Fe^{+++}. More correctly we might say that there are fewer possibilities of formation of unabsorbable compounds. If, however, the greater amount, or all of absorption normally occurs in the stomach, and possibly the upper duodenum, the form in which the element is present would seem more or less inconsequential. The writer is of the opinion that the latter state of affairs actually obtains under normal conditions.

It is true that some of the difficulties encountered in iron therapy due to poor absorption may be obviated by the introduction of the element by other routes. Parenteral, intramuscular, and intravenous administration have received considerable attention. Heath, Strauss, and Castle (43) found that a daily dose of 1 gram Fe as ferric ammonium citrate orally is approximately equivalent to a daily dose of 32 mgm. of Fe given parenterally in the same form to patients with hypochromic anemia. The amount of Fe given by the latter route corresponded closely to that gained in circulating hemoglobin and was apparently utilized to a great extent. Eveleth, Bing, and Meyers (26), as well as Beard and Boggess (6), obtained similar results in treating rats having nutritional anemia. Others (35) found that intraperitoneal injection of Fe in doses of 5 mgm. at three-day intervals combined with one or two transfusions of blood seemed to be of value in treatment of secondary anemia of infancy.

Robscheit-Robbins and Whipple (85) have shown that injection of colloidal ferric hydroxide is followed by a quantitative return of the Fe as hemoglobin in the anemic dog. It has recently been claimed (89) that ferrous adenylate provides a stabel, readily soluble, non-toxic form of iron for intramuscular or intravenous clinical uses.

Parenteral iron administration is often associated with a great degree of discomfort to the recipient. Many feel that danger accompanies the intravenous administration of colloidal iron. The writer has failed to note any untoward reactions following the use of the latter in the course of a series of long experiments. The danger is probably of the same magnitude as exists among any agents used intravenously, and earlier experiences by others in which pulmonary emboli were a common aftermath (79) were probably referable to the quality of the preparations used.

Although one would not too readily recommend intravenous iron therapy except in especially indicated cases, nevertheless, the recent statement of Seward (93) is hardly justified: "Iron is still given by injection . . . , but it is useless, may be toxic, and is certainly expensive."

Experimentally, these methods are of great assistance in studying the path of iron in the body. One must keep in mind, however, the different mechanism of removal of iron from the bloodstream when given intravenously in the colloidal form as compared with the oral administration of iron compounds.

The *storage of iron in the body* is by no means well understood. Its study has been obscured principally by the methods employed. It is futile to attempt to follow the deposition of iron in tissues which are bathed in blood much richer in iron than the tissues proper. This fact was recognized as early as 1886 by Zaleski (123) who studied the iron content of livers of a wide variety of animals using both gravity perfusion and viviperfusion methods. Strangely enough, such an excellent example was not followed for a long period of years and, even today, one not infrequently finds that unperfused fresh tissue are analyzed for iron in the estimation of storage under experimental conditions. The changes in the iron content of tissues following administration are sometimes very small, but nevertheless, significant, and would not be detectable in other than blood-free material (8, 10, 16, 25, 39, 50, 55, 66, 99, 111).

In the normal animal the tissue iron storage may be extremely variable, especially that in the liver, spleen, and bone marrow (10). It is seemingly related to the previous diet and, if we are to study the changes which take place under treatment, we must have a dependable base line from which to determine the variations. Such a base line has been established by an extended period of anemia with a concurrent restricted iron intake (10, 39).

When we consider the problem of iron storage in the body we must begin by recognizing the different forms in which this element may occur in tissues. That iron in some form is present in all cells, has been shown spectographically by Fox and Ramage (30). The bulk of iron is present under normal conditions in the combined form of hemoglobin. Part of this hemoglobin iron is incorporated in the red blood cells and upon it is dependent the respiratory function of the cells. In the normal individual this fraction constitutes about 55 per cent of the body iron. It may, however, vary over a considerable range, being extremely low in severe cases of hypochromic anemia and relatively high in polycythemia. Recent reviews cover the clinical features of these changes (9, 36, 106, 107).

Another important fraction of hemoglobin iron is found as the non-circulating compound in the striated muscles. Muscle hemoglobin is very similar to blood hemoglobin in that it gives the same spectrophotometric absorption curves (56), and contains the same amount of iron (108). Like blood hemoglobin it yields bile pigments when given intravenously, intraperitoneally, or intramuscularly (118). It may be differentiated from blood hemoglobin by means of a specific precipitin reaction (44). Muscle hemoglobin has been shown to be dependent on the age and activity of the animal. Prolonged severe anemia may lower it slightly, but exercise is more important than anemia in determining the level of this pigment (115).

However, only about half of the iron contained in the perfused striated muscle can be accounted for as combined in muscle hemoglobin (39). The remainder corresponds in amount to the iron of the body tissues following depletion of the readily available stores. Such iron has been referred to as the parenchyma iron and varies in quantity from about 1 to 3 mgm. per 100 grams of fresh tissue. Muscle hemoglobin and parenchyma iron are inviolate stores of iron which are not drawn on no matter how great the emergency due to anemia (39, 50).

It might be of interest to note the distribution of iron in the body. The values below were arrived at from analyses of perfused dog tissues (10, 39). Variations among animals in the striated muscle fraction are of course very great (115) and other individual differences may make only an approximation possible.

For a dog of 20 kgm. body weight let us assume a circulating blood volume of 1500 ml. and a bulk of striated muscle of 6.5 kgm.

	mgm.	*per cent total body iron*
Blood hemoglobin iron	900	57
Muscle hemoglobin iron	110	7
Total hemoglobin iron	1010	64
Parenchyma iron (muscle and other tissues)	240	16
Available visceral storage (liver, spleen, and marrow)	225	15
Available iron of other tissues (estimated)	75±	5±
Total iron	1550	100

Thus there are 270 grams of hemoglobin circulating and an available iron equivalent to 90 grams hemoglobin which could be supplied as needed. Therefore the dog has about a 33 per cent reserve supply of hemoglobin. Of the important iron fractions in the body we might say that 65 per cent is combined as hemoglobin, 15 per cent as functional iron of the tissues (parenchyma iron), and 20 per cent as storage available for body needs.

Small quantities of iron are found in the blood serum. Methods now generally in use do not lend themselves to the determination of the absolute amount of this iron accurately, but at least can be used to show variations from the average. In general investigators (6, 29, 63, 73, 83) are in agreement with the findings of Barkan (5) who has contributed extensively to the study of this small but perhaps important fraction. The iron is present to the extent of about one microgram per milliliter of serum (one part per million). It is usually elevated in pernicious anemia, but upon remission, drops to normal. Low values usually associated with the hypochromic anemias are raised upon feeding iron salts.

The iron content of whole blood has received a great deal of attention. In 1898 Aberhalden (2) reported finding more iron in the blood than could be attributed to hemoglobin. The discrepancy he found reached as high as 10 per cent in some cases. Barkan (5) has revived interest in the subject. Many admit the existence of nonhemoglobin iron as an entity (5, 51, 58, 101, 109). As such it would render the calculation of blood hemoglobin from the whole blood iron unwarranted. On the other hand a number of workers find good correlation between the values for iron and hemoglobin (37, 45, 48, 55, 75, 90). The discordant evidence perhaps can in part be traced to the methods in use for hemoglobin estimation (78). The existence of non-hemoglobin iron can hardly be denied, however, in the light of the work reported. Its level seems to constitute more of an individual than a pathological characteristic, not being affected by most procedures which ordinarily influence other iron fractions. The non-hemoglobin iron of the red blood cells is considerably greater in quantity than serum iron.

Of particular interest is that important part of the body iron which may be designated as *available storage.* By this we mean available for the needs of the body such as the production of new hemoglobin. This term probably cannot be applied to non-hemoglobin iron of the red blood cells, as it has never been conclusively shown that the levels of such iron are affected by the demands of anemia. Certainly it is not applicable to parenchyma iron of the striated muscle or other tissues (39).

The chief depots for the storage of iron include the liver, spleen, bone marrow (39, 66, 96, 109) and, under some conditions (10, 74, 77) the kidneys. These tissues vary widely in their capacity for storage. The spleen may hold more of the element per unit of weight of the organ than any of the others, but, in view of the comparatively small bulk of tissue involved, cannot take up as large absolute amounts as the liver and marrow. Then, too, it must be remembered that a considerable portion of the iron found in the spleen, as usually analyzed, occurs in red cells contained in the sinusoids.

Many investigators have studied storage of Fe in these tissues, but, inasmuch as most of the work was carried out on unperfused material, it would not help to clarify the problem by including too comprehensive a survey of their findings. Some of the more important material is discussed below.

The storage of iron in the normal perfused animal is greatly dependent on the diet as was shown by Bogniard and Whipple (10). They suggested periods of anemia of two or more months' duration as a means of depleting the stores to establish a base line for the further study of storage. From their work it would appear that the chief depots are the liver, spleen, and marrow.

It has been known for a long time that there is an increased amount of iron in the livers of newborn infants. Ramage (81), in studying the metallic content of livers of children and fetuses, found that the percentage of Fe is quite constant, while the total iron increases to shortly after birth, and then suffers a decrease to two years of age, followed by an increase. This fall following birth is due to the low iron content of milk.

Gladstone (33) finds a rise in the iron content of children's livers during the first two months after birth which he attributes to storage of Fe set free by post natal blood destruction. The sharp drop during the remainder of the year, he feels, is caused by demands on the Fe reserve by hemoglobin formation and body growth.

When in disease or for other reasons, hemoglobin is liberated in the circulating blood, the iron may be stored partly or in full by certain tissues. Barcroft and Barcroft (4) showed that the spleen is the chief depot from which red cells are added to the circulation in an emergency. They estimated that enough red cells could be extruded from the spleen to increase the circulating hemoglobin by 25 per cent. This organ is also known to take up liberated hemoglobin. Its capacity to do this is, in part at least, ascribable to the reticulo-endothelial tissue in this organ. In a similar way the liver and bone marrow act to remove iron from the blood stream. In acute hemolytic anemia in rabbits, attended by destruction of more than one half the blood in three days' time, nearly all the iron from destroyed hemoglobin has been found to be deposited in the liver, spleen, and kidneys (74).

It has been suggested that the spleen is more active in furnishing available iron than the liver, through its capacity for the destruction of red blood cells (62). In normal dogs on a diet adequate in iron, removal of the spleen brings about a temporary increased loss of iron from the body which is most marked during the period of developing anemia (121).

It has been found in studying the conservation of blood hemoglobin in dogs following intravenous injection that a pigment giving a positive stain for Fe was found in the liver and spleen, and when the minimal renal threshold was exceeded, there was a deposition of the pigment in the epithelium of the renal convoluted tubules. Anemia, due to bleeding, resulted in the rapid removal of this pigment showing conservation of material for the construction of hemoglobin. Muscle hemoglobin, on the contrary, did not, on injection, cause a deposition of pigment in the tubules (77).

Polson (79) followed the fate of colloidal Fe administered intravenously in rabbits. He found that the greater part was held in the liver, spleen, and lungs. In the last the iron was present as emboli; in the liver and spleen, it had been ingested by the endothelial cells. He found that iron did not accumulate in the spleen on feeding, or injection by subcutaneous or intraperitoneal routes, as it did when given intravenously. Unfortunately, he did not use perfused tissues, so the quantitative value of his figures is relative. The emboli were probably due to the quality of iron injected, as others have failed to record such findings (39, 85).

There are probably storage places for iron other than the liver, spleen, and marrow. Hahn and Whipple have shown that only a little over half of intravenously injected colloidal iron can be accounted for in these perfused tissues (39), even though similar quantities would eventually be turned over to new hemoglobin if sufficient time were allowed to elapse (85). Therefore, although the iron was known not to have been eliminated, it escaped detection by the methods employed.

In the past few years the work of Hart, Steenbock, Elvehjem, and their associates (22, 41, 110) on nutritional anemia in rats has aroused an interest in the effect of copper on iron metabolism. They found that the administration of pure iron salts alone to rats subsisting on a milk diet did not prevent or cure the anemia, but that the addition of a trace of copper was necessary. These findings have been corroborated by many others (16, 47, 50, 57, 87, 96). It would seem that the action of the copper is concerned with the metabolism of the iron in the liver since, in the absence of copper, iron is found to be stored in this organ but is not utilized (16, 50).

There is other evidence that copper is related to iron metabolism. Its level in the blood (34, 60, 91, 92), liver and spleen (38) varies indirectly with the iron content under many anemic conditions.

The amount of copper required is so small, however, and its occurrence in foods so widespread (20), that *from a practical standpoint there is no indication whatsoever for the inclusion of this element in anemia therapy.* The possibility of a copper deficiency occurring in humans is exceedingly remote, if it exists at all.

Many investigators have studied iron balances in man in an endeavor to fix the daily requirements of the individual. An intake of about 10 mgm. per day or even less is probably sufficient for the normal adult (27, 82). Requirement for growth has been placed variously at from 0.2 to 0.6 mgm. per kilogram daily (17, 59). In pregnancy the need for iron is increased, not only for maintenance of the maternal organism (the placenta, adnexa and circulation therein), but for the fetal blood and tissues, and the fetal reserves for post natal growth. The requirements are greater therefore than are shown merely by a positive balance and have been estimated at about 15 to 20 mgm. per day (14). Fullerton in an extensive study of iron metabolism in relation to menstruation and pregnancy feels that during the period from conception to six months postpartum a positive iron balance of 2 mgm. per day is needed (31).

A review of the iron requirements in nutrition is to be found in Sherman's recent text (97).

Some workers have attempted to measure the "availability" of iron in various foods (23, 94, 98) according to the amount of the total iron which reacts with di-pyridyl (47). This reagent does not react with hematin iron. They would fix the blame for poor absorption of iron containing materials on the existence of a part of it as hematin. It is quite true, as has been pointed out, that the latter is poorly if at all utilized when fed. However, the iron salts themselves, although reacting with di-pyridyl, are not often utilized even under the best conditions to a greater extent than about 40 per cent (85). The utilization of the element itself is greatly dependent on the level at which it is fed. We therefore will have gained but little by referring the relative availability of iron in foods, some of which in themselves are potent as hematopoietic agents, to iron itself.

Concerning the path taken by iron in the body during the process of being incorporated into hemoglobin and parenchyma iron we can say little with certainty. In spite of the great amount of investigation of this element, the problem because of its apparent complexity is but slightly clearer than a decade ago. Some progress is being made but unfortunately certain phases, chief among them the influence of copper on iron metabolism, have been greatly overemphasized.

As has been stated, many feel that absorption depends upon the existence of iron in the ferrous state (67, 104, 102) with subsequent oxidation to the ferric state in the blood where it is transported combined with globulin (103) to the liver. Whether this reduction and oxidation is necessary seems open to question. It may be absorbed from the stomach or duodenum as ferric iron and transported as such. It remains to be seen whether the serum iron represents such iron in its path to the liver.

Upon reaching the liver, storage takes place up to a certain point (10). The capacity to store iron by this organ appears not to be readily exceeded (39) except in disease (64, 95, 32) in which case perhaps we cannot consider it storage in the strict sense of the word. An excess may be removed in part by other tissues, the spleen, marrow, and under some conditions the kidneys. All tissues normally appear to have a moderate amount of iron over and above the irreducible parenchyma fraction (10, 50, 39) and inasmuch as it is readily depleted in anemia it can be looked on as storage. Iron is eliminated in the bile (52) although this may not be the only path of excretion governing the body iron level under normal conditions. The kidneys play only a small part if any in its excretion normally. It has long been thought that the large intestine is the chief excretory organ for the element since urinary iron is not readily changed by dietary factors. Recently, however, Welch, Wakefield and Adams, studying the iron balance in a patient with an ileostomy stoma and an isolated colon, have shown that the iron excretion by the colon is negligible (113).

In the event of a need for iron, as a result of dietary restriction, or anemia, the depots readily give up their stores. When these are exhausted the body tissues are maintained with their parenchyma iron first at the expense of blood hemoglobin production (39, 50), and finally growth (50). When iron is fed under these conditions it is whisked through the liver very rapidly. Whether the iron in its passage through this organ is modified in any way or is partially built into hematin precursors is not known but is suspected. About half of the iron in the perfused rat liver has been found not to react with di-pyridyl indicating a considerable amount of hematin or similarly bound iron (66). It seems reasonable to suppose that the intermediates or unmodified iron as the case may be are then transported to the marrow for the final elaboration of the hemoglobin. It is conceivable that the last stages are accomplished in the immature red cell itself although there is no direct evidence that such is true.

When the body stores have been depleted in anemia iron administered is first used to supply the deficit in circulating hemoglobin (39, 50) following which the excess is stored. This storage in the dog has been shown as an amount of iron equivalent to 40 to 70 grams hemoglobin per 10 kgm. of body weight. Realizing that values obtained from the tissues of different species may vary considerably, one might estimate an iron reserve in the human corresponding to upward of 250 grams of hemoglobin.

The red cell having completed its life cycle the iron in whole or part is recovered from the fragments in the spleen and thence recirculated, again to undergo transformation into respiratory pigment.

Little has or can be said concerning the nature of parenchyma iron. Whether part or all of it is of a hematin nature (cytochrome) has yet to be divulged. Its origin and fate remain a mystery although its functional importance can hardly be questioned when we see how tenaciously the body holds it.

About the same can be said about our knowledge of the origin of muscle hemoglobin. The latter has been shown to give rise to bile pigments (118) but the course taken by the iron in this degradation is not known.

A complete knowledge of the transformations which iron takes in the animal body during its absorption, storage, fabrication into its several working forms, liberation, conservation, and excretion, will probably not be forthcoming very soon. It is an exceedingly complicated problem and will likely continue to offer a challenge to investigators for some years to come.

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THE ANEMIA OF IRON DEFICIENCY

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INTRODUCTION

In the study of deficiency disease, investigative medicine seeks to identify the deficient substance and to describe the part which it plays, eventually putting the deficiency and its supply upon a quantitative basis. The facts, crude as they are, are sufficiently proven at the present time to allow us to describe iron deficiency quantitatively. When iron is administered parenterally to cases of iron deficiency, it can be recovered quantitatively in the new-formed hemoglobin. Iron is a metal and, unlike certain organic substances of the food which are necessary to the body, such as the vitamins, it is not destroyed or used up in the body, but is conserved and if not excreted can be utilized again and again. These basic facts are essential in any adequate consideration of iron deficiency.

Iron deficiency is common in man and is characterized by hypochromic anemia. It may be rightfully classified as "secondary anemia," although that term is outmoded and is rendered meaningless by modern knowledge of the etiology of anemias.

It is not within the limits of the present communication to make a complete review of the modern literature concerning iron and anemia. The purpose of the authors is to bring together what seem to be the more significant obervations in this field. It is also their purpose to explain a thesis which will aid in clarifying the subject and assist the clinician in explaining and interpreting the etiology of anemia due to iron deficiency, separating it from other anemias. The conclusions will be based not only upon the literature but also upon material drawn from many cases, including more than 300 thoroughly studied cases of anemia responding to iron.

HISTORICAL NOTE

The history of the medicinal uses of iron goes back to the very beginnings of western medicine and is a relatively untilled field. For short historical reviews the reader is referred to the articles of Christian (36) and Fowler (66), and to certain of the monographs cited in the bibliography.

Iron has seemed to attract false theorization and to repel true experimentation. As Whipple aptly expressed it, "iron is an elusive sprite." Its value has been approved and condemned many times. It was only by a slow and jerky process of brilliant discoveries, doubts, faulty theories, good and bad deductions from experiments, and broad clinical experience extending over several centuries of time that the present-day point of view was reached. It is a tribute to the versatility of the human imagination that iron was employed successfully long before any certain foundation for its use was discovered. Iron and steel meant strength and power in battle. In older pharmacopeias iron is referred to as mars. The name of Sydenham seems an important one in the early literature on iron, for he, in 1661, recognized the value of iron in the cure of chlorosis (201). Not until Menghini in 1746 (136) called attention to the presence of iron in blood could there be a logical explanation of its value. In 1832, Blaud, a name known to the public, announced the formula and dosage of a preparation of iron used successfully in the treatment of chlorosis (16). It is typical of the history of iron that the original dosage of Blaud's pills was reduced by certain physicians. A year after he had announced his observation, Blaud objected to the use of a dose smaller than he had recommended (17). Today we know the value of large doses of iron and the relative ineffectiveness at times of small doses.

The discovery of Menghini and the demonstration of the value of large doses of iron in anemia seem fundamental in the light of modern knowledge of iron deficiency. A third fundamental discovery came with the development of methods of counting erythrocytes and determining the hemoglobin concentration. To Duncan (51) and Hayem (81, 82) perhaps, goes the credit for first observing what we would today term a lowered color index in anemias responding to iron. Osler in 1885 (162) mentioned that after hemorrhage the development of the hemoglobin does not keep pace with that of the corpuscles so that the latter may have a lowered hemoglobin percentage, indicated under the microscope by a paleness of the cells. The proportion of the hemoglobin to the number of red blood corpuscles was recognized in Laache's monograph (114) as an important factor in differentiating the anemias. These observations confirmed a laboratory method of determining in advance the kind of anemia which would probably respond to iron.

Even in modern times the value of iron in the treatment of anemia has been doubted. The disproved theory of Bunge (27) and Abderhalden that organic iron preparations should be more effective than inorganic was partly responsible for this. Experimental work showed the ineffectiveness of iron in anemia not originating from iron deficiency (215, 211). Meulengracht (140) and Barkan (8) were among the first in the present century to stress the importance of giving large doses of iron. With the revival of interest and knowledge in the therapy of different kinds of anemia, following the studies of Whipple upon the dietary factors which promote hemoglobin regeneration in dogs and the discovery of the value of liver in pernicious anemia by Minot and Murphy in 1926 (148), iron as a specific remedy seems to have been established permanently.

IRON IN NORMAL PHYSIOLOGY

I. Distribution in body

Iron is known to be present in most, if not all cells, both plant and animal (151, 103, 68). Jones (103) stated that "inorganic iron is more widely distributed throughout the animal and vegetable tissues than is generally realised." It is probably present most constantly, however, in the form of complex organic compounds in protoplasm. Jolly (102) mentions iron occurring in the nuclei of cells. It is apparently an essential element in various pigment substances distributed widely in nature, not only hemoglobin, but also other pigment substances situated within cells, which appear to control at least to some degree the most important chemical activities within living cells (186). According to Sherman (186) the normal adult human body contains about 3.0 grams of iron. Most of the iron present in the human body is an essential constituent of hematin or heme, the iron pyrrol part of hemoglobin whose chief function is to transport oxygen from the lungs to the tissues. Pigment complexes related to hematin and known as "cytochrome," are present in a variety of animal tissues (4). Another iron-containing pigment, myohemoglobin, whose absorption bands are nearly or quite identical with those of blood hemoglobin, is an important substance in active muscle tissue.

For the purpose of clarifying the clinical approach to the problem, *iron may be considered to be present in the body in three different states from the point of view of their relations to circulating hemoglobin: as an essential part of hemoglobin, as latent iron stored in depôts for emergency uses, and as tissue iron unavailable for blood formation.*

The estimation of the amount of hemoglobin is important from the point of view of iron deficiency anemia because it gives us fundamental information of the amount of iron in the body. It is not appreciated ordinarily that the blood contains iron in relatively huge proportions compared to other tissues of the body. The following table of values derived from various sources will suffice to illustrate this point (table 1).

TABLE 1

Approximate amounts of iron per 100 grams in blood and various tissues of the body

	IRON *gram*
Whole blood	0.053
Plasma	0.006
Liver	0.010
Spleen	0.020
Muscle	0.005
Kidney*	0.003
Brain*	0.002

* Analysis of Kennedy (113) upon dog tissue.

The total amount of iron in the circulating blood of a normal adult man may be estimated at 2.65 grams if he has 15.6 grams of hemoglobin per 100 cc. of blood, and a blood volume of 5000 cc.

Peters and Van Slyke state that "the precise ascertainment of the Fe content of purified human hemoglobin is a problem that awaits solution" (168). Since the direct determination of the amount of hemoglobin seems at present an impossible task, there remain chiefly two quite accurate methods for the relative estimation of hemoglobin: the determination of the iron content of blood, and that of the oxygen capacity of blood. Since the amount of hemoglobin which contains one atom of iron combines with one molecule of oxygen, these two methods agree very well (113). Hüfner in 1894 (100) found that 100 grams of ox hemoglobin contain 0.34 gram of iron. More modern determinations of the amount of iron in human hemoglobin are in close approximation to this figure (Butterfield, 0.335 per cent (28); Sachs et al., 0.335 per cent (179); Fullerton et al., 0.333 per cent (71)).

The amount of hemoglobin has usually been calculated from the oxygen capacity of blood employing Hüfner's factor of 1.34, obtained from the carbon monoxide combining power of ox blood. Thus, Haden (76) and Osgood (161) and others in this country have employed as a standard for the average adult man an oxygen capacity of the blood of 20.9 volumes per cent, which is equivalent to $\frac{20.9}{1.34}$ or 15.6 grams of hemoglobin per 100 cc. of blood. Different standards for the "normal" hemoglobin content of the blood or "100 per cent" hemoglobin are in use in different parts of the world. For example, in England the figure of Price-Jones (171) is in use: 13.8 grams of hemoglobin per 100 cc.; in Germany (185): 15.0 grams of hemoglobin per 100 cc. Therefore, although there is no definite agreement as to what constitutes "100 per cent" hemoglobin, there is agreement as to what is meant by grams of hemoglobin, which is nevertheless based on a rather empirical standard. Simple colorimetric methods for the clinical determination of hemoglobin, for example the method of Sahli when standardized, give results which are in fairly good accordance with oxygen capacity and iron determination (49).

The second state in which iron may be considered to be present in the body is as latent or stored iron. Whipple and Robscheit-Robbins (211) have shown that there is a large store of reserve material capable of use in regenerating hemoglobin in bled dogs upon a standard ration. Iron must have been an important part of the reserve material in these dogs. Various authors have administered iron orally or parenterally to animals and have found iron deposited chiefly in the liver, spleen, lymph nodes, kidney, and bone marrow (215, 216, 157, 169, 170, 158, 77). In certain circumstances the percentage of iron in the liver and spleen may equal that in the blood. It is well known that in certain human anemias such as hemolytic jaundice and pernicious anemia in relapse, an excess of iron apparently derived from broken-down hemoglobin, is found chiefly in the liver and spleen. Even the skin may contain a store of available iron (64). Such iron is readily available for hemoglobin formation when blood regeneration takes place. It is probably, for the most part, readily detectable in the tissues by simple iron stains, whereas the iron in the tissues which is apparently not available for hemoglobin formation, is in a bound form which is unstainable except after special treatment which breaks down the organic combination (134).

The amount of iron stored in the human body which is available for hemoglobin formation can only be roughly estimated. It undoubtedly varies considerably with age, sex, nutritional state and previous circumstances which have called it into use. It is certainly a common clinical experience to observe individuals who have had severe acute gastro-intestinal bleeding and whose hemoglobin has been reduced below 50 per cent, regenerate hemoglobin to normal proportions even though no iron medication has been given and the diet has contained a reduced amount of iron. For the sake of arriving at some sort of estimation of the available iron stores, it is not unreasonable to assume that an adult man in good nutritional state can lose about one-half his circulating hemoglobin and recover this completely without recourse to iron therapy. If the total amount of iron in his circulating blood were 2.65 grams (see above), he would have lost 1.32 grams of iron and utilized the same amount from the available iron stores. A certain amount of these reserve iron stores may be considered to be present in the hemoglobin of extra-circulatory new-formed red blood cells lying functionless in the bone marrow. The actual amount of such available iron can not be estimated accurately, although the total amount of iron in the bone marrow is probably of the same order of magnitude as the total iron in the liver (77). Following exhaustion of the iron reserves in the dog by bleeding, the iron content of the skeleton diminishes considerably (64).

Lastly, iron may be considered to be present in the body as tissue iron unavailable for blood formation, that is, the iron in close combination with intracellular substances which have to do with essential vital functions of the cells. Probably there is no sharp line of demarcation separating iron stores from unavailable tissue iron. The latter is undoubtedly conserved by the body for further use when cells die and are broken down. Very little is known of the total amount of this iron in the body or how it may vary in different circumstances. Josephs (105) from work upon rats, has estimated the unavailable tissue iron to be about 5 mgm. per kilogram of body weight. The estimation of Hahn and Whipple (77) in the organs of anemic dogs would give a figure somewhat lower than 5 mgm. If this figure is used for a man weighing 65 kgm., the unavailable tissue iron would equal about 0.325 gram. Adding together the total circulating blood iron, the iron available in stores and the unavailable tissue iron we have the figure 4.3 grams for the total amount of iron in the body of a man in good nutritional state. This figure is considerably higher than the 3 grams estimated by Sherman (186). It corresponds to that published by the White House Conference on Child Health and Protection (214). Fontes and Thivolle (64) have estimated that in the dog four-ninths of the iron is present in the circulating hemoglobin, and five-ninths in other tissues of the body. This calculation would give a figure of about 5.6 grams for the iron content of the body of an adult man.

II. Iron metabolism and the requirements for physiological exogenous iron loss

Iron is excreted almost entirely by the bowel. It is absorbed probably in large part by the upper small intestine. The exact sites of absorption and excretion are unknown. M'Gowan (126) has reviewed this subject and has concluded that "there would appear to be no justification for the statements current regarding the movements of iron in the body, namely, that while absorption takes place solely from the duodenum, excretion is limited to the large intestine. At the same time nothing is known regarding the path of absorption of organic 'food' iron." He was of the belief that absorption and excretion could occur at the same sites in the intestine, and that histological demonstration of iron in the wall of the intestine did not give information as to whether it was being absorbed or excreted. However, the observations of Schmidt (182) seem significant. In mice rendered extremely anemic by a diet low in iron maintained for 3 or 4 generations iron appeared to be absorbed first at the tips of the duodenal villi.

It is not clear in what form the iron of the food is absorbed. That the nature of the contents of the stomach and duodenum are favorable to the absorption of both food iron and inorganic iron preparations is apparent from the work of Starkenstein (187), Reimann and Fritsch (174) and Lintzel (121). The acidity of the stomach and duodenal contents favors the formation and preservation of ferrous ions and prevents the formation of insoluble iron compounds. Fontes and Thivolle (64) considered that therapeutic iron is absorbed only in the ionized state. (For further reference to the absorption of inorganic iron see pages 332ff.) Höber (96) maintained that iron has a peculiar position in absorption in that it is apparently absorbed intraepithelially along with lipoid substances, whereas lipoid insoluble substances, salts and sugar are absorbed interepithelially. This would make it appear that iron resorption is a function of living epithelial cells. This point of view appealed to Lintzel (121) whose work upon iron metabolism under various conditions tended to show that the body could assimilate or reject iron depending upon the needs for iron, a consideration which the work of Fontes and Thivolle (63) on dogs seemed to corroborate. Iron is apparently transported in the body as plasma iron (149). The plasma iron increases after the administration of large doses of iron and diminishes during very active erythropoiesis, for example, during the reticulocytosis in pernicious anemia following liver extract.

The iron content of the normal human urine is very small. Lintzel regards it as negligible, less than 0.02 mgm. per liter (121). Marlow and Taylor (135) found values for urinary iron ranging from 0.03 to 0.8 mgm. per 24 hours. Lanyar, Lieb and Verdino (116) found less than 0.01 mgm. of iron per liter of urine in normal urine and in certain blood diseases. The tendency of the body to retain iron is reflected by the fact that the kidneys do not excrete increased amounts of iron even when iron seems to be present in excess in the system. The iron content of the urine is not increased after the administration of inorganic iron by mouth (135, 121, 116), or, at least to any distinctive degree, after increased destruction of red blood cells by phenylhydrazine (176, 7). An exception is potassium ferrocyanide which will be eliminated in the urine when administered orally or parenterally (121). The iron content of the urine may be increased moderately following the administration of inorganic iron compounds parenterally (116).

Very little is known of the internal metabolism of iron which must take place during the normal processes of destruction and formation of red blood cells. The storage of iron has already been discussed. Although the liver must play an important part in the intermediary metabolism of iron, the bile contains only very small amounts of iron (121). It is possible, however, that the bile may be an important factor in the absorption of food iron in the intestine.

Sherman (186) has estimated the "dietary standard" of man to be about 12 mgm. of iron per day. This figure corresponds roughly with the iron content of the daily diet of adults in this part of the world (97). It is very difficult, however, to ascertain exactly what the iron intake of an individual should be to maintain adequate iron stores above the physiological needs. The figure would vary in the two sexes and at different ages. The minimum iron requirement of the diet must satisfy the physiological requirements of the body; it must take into account the iron of the food which is unavailable for absorption and is therefore lost in the feces; finally it must include what is needed to replace the iron lost by the exogenous metabolism. The available iron of foods has been estimated by Elvehjem, Hart and Sherman (54) by the dipidryl method and they found that the available iron so determined corresponds to the amount of iron of the food available for building hemoglobin in anemic rats. They estimated that 47 per cent of the iron in wheat and yeast and 57 per cent in oats was available. Iron retentions from the food may be shown in metabolism experiments to reach as high as 50 per cent under circumstances in which there is a special need for iron by the body (see table 2, the observations of Leichsenring and Flor. (118)).

The amount of iron which may be lost by daily exogenous metabolism and the amount of iron of the diet which would be needed to cover this loss is very difficult to ascertain with any accuracy. The loss of iron by this means is apparently very small indeed, and is undoubtedly covered very adequately even by diets which would be considered very low in iron. The work of Lintzel (121, 120) has elucidated this problem. Lintzel pointed out that the iron lost during fasting is relatively large in man (see table 2) and in animals, but that this iron is probably to be accounted for by tissue breakdown. When he fed normal men a diet which was low in iron but with adequate caloric content, iron balance was reached in a few days. Even when the diet contained as little as 0.9 mgm. of iron daily, the feces in a few days contained the same amount. The amount of iron in the urine he considered negligible. He therefore concluded that the iron need of adult man was less than 0.9 mgm. per day.

In table 2 is given a summary of certain modern studies upon the iron metabolism in different conditions. For contrast, the work of Lehmann, Mueller, Munk, Senator and Zuntz (117) upon two professional fasters is included. The work of Farrar and Goldhamer (59) seems to bear out that of Lintzel. These authors found that 3 adult men and one woman were in iron balance while receiving quite reduced amounts of iron. One man received a diet for 316 days containing an average daily iron content of 4.9 mgm. During the last 31 days of the period of observation, while the diet contained 5.2 mgm., this man was in iron balance, and he had no demonstrable anemia. It was concluded that the iron requirement of the normal adult male is not more than 5 mgm. daily. The finding of Reznikoff, Toscani and Fullarton (176) that their patient, a middle-aged male, retained an average of 5.6 mgm. of iron daily over the course of 132 experimental days is at variance with the work of Lintzel and of Farrar and Goldhamer. It is possible, however, that this individual who had recovered from a deficiency syndrome previous to the experimental period may have had an unusual need for iron. The work of Ohlsen and Daum (159) upon 3 normal women, which included the loss of iron in the menses, showed that with an intake of about 14 mgm. per day there was a slight average daily loss of iron of a little over 1 mgm. Leverton and Roberts (119) showed that 4 young adult women were approximately in iron balance while consuming food somewhat reduced in iron. Other workers (see table 2), studying infants, children and pregnant women, have shown, as is to be expected, that

TABLE 2

Summary of studies upon iron metabolism

AUTHORS	CONDITIONS	DAILY INTAKE OF IRON	DAILY OUTPUT OF IRON	DAILY IRON BALANCE
		mgm.	*mgm.*	*mgm.*
Josephs (105)	Normal infants. Milk diet			
	(1) Birth to 2 months			−0.01
	(2) 2 months to 4 months			+0.12
	(3) 4 months to 6 months			+0.18
Wallgren (207)	5 normal infants aged 3 weeks to 11 months. Breast milk			+0.18
Ascham (5)	6 preschool children, weight 17.1 to 19.3 kgm. 90 experimental days	10.67	9.41	+1.26
Leichsenring and Flor (118)	4 children, aged 35 to 56 months			
	20 experimental days	3.25	2.07	+1.19
	20 experimental days	6.50	3.29	+3.21
Daniels and Wright (42)	8 children, aged 3 to 6 years. 80 experimental days	10.89	7.81	+3.08
Farrar and Goldhamer (59)	Normal adult male	5.2	5.4	−0.2
	Normal adult male	7.7	7.8	−0.1
	Adult male. Minimal tuberculosis	7.3	7.4	−0.1
	Normal adult female	8.3	8.2	+0.1
Reznikoff, Toscani and Fullarton (176)	Middle-aged male, recovered from deficiency syndrome. 132 experimental days	18.4	12.8	+5.6
Ohlsen and Daum (159)	3 normal women. 56 experimental days	13.78	14.95	−1.17
Leverton and Roberts (119)	4 normal women 440 experimental days	11.81	11.12	−0.69*
Lintzel (120)	Normal men			
	(1) 16 experimental days	58.5	58.2	+0.3
	(2) 49 experimental days	12.7	12.8	−0.1
	(3) 16 experimental days	2.5	2.4	+0.1
	(4) 3 experimental days	0.9	0.9	0.0
Coons (37)	9 women, from eleventh week of pregnancy to term	14.72	11.56	+3.16
Lehmann, Mueller, Munk and Senator (117)	Stool examinations on two fasting men			
	(1) Cetti, 10 days	0	7.3	−7.3
	(2) Breithaupt, 6 days	0	8.0	−8.0

* After blood loss from menses and venesection was taken into consideration the subjects were approximately in iron balance.

there is an average daily retention of iron in these subjects. During the first few weeks of life there is a negative iron balance (105, 190).

A survey of table 2 will lead to the supposition that an appreciably negative iron balance can not be demonstrated, even when the diet is very low in iron except in conditions of tissue breakdown, such as fasting. A positive iron balance is demonstrable when there is growth or pregnancy.

III. Physiological iron requirements

The normal physiological iron requirements of the male are for the needs of growth, of the female for the needs of growth, menstruation, pregnancy and lactation. In addition to these requirements there are the theoretical requirements for exogenous iron metabolism which have been discussed in the preceding section. Pathological requirements for iron, which are in the main confined to pathological blood loss are to be considered in the principal subject: iron deficiency.

In tables 3 and 4 and figure 1 are shown the normal physiological iron requirements of the male and female. These include the iron needed to supply the total circulatory hemoglobin, the non-available tissue iron (extra-circulatory iron) which increases with growth, and the losses of iron caused by menstruation and pregnancy. The iron requirements for the reserve store of latent but available iron are omitted. If they were included, they would make up a small but important increment of iron in each age group—for example, in the male during growth an annual average iron requirement of about 0.07 gram if the adult iron store were considered as 1.32 grams.

Sources of data employed in constructing tables 3 and 4

The data presented in tables 3 and 4 are gathered from various sources and are only approximate. It is felt, however, that they supply dogmatic information which will be helpful in reaching logical conclusions and in understanding some of the iron-responding anemias, particularly those which are commonly observed in children and in women. During growth, the building of the increasing circulatory hemoglobin is the chief requirement of iron. Therefore, the first 8 columns were devoted to this subject. The blood volume was determined from the surface area at the different ages and the total circulating hemoglobin was determined from the product of the average grams of hemoglobin per 100 cc. and the blood volume. Hemoglobin was considered to contain 0.34 per cent of iron.

The birth-weight was obtained from Holt and Howland (98). The weight and height statistics from ages one to 20, at which time growth was assumed to cease, are those of Gray and Ayres (72). The body surface was calculated up to 25 kgm. from the Benedict and Talbot modification of the Lissauer formula (11), thereafter from the Boothby and Sandiford tabulations of the DuBois Body Surface Chart which is commonly used for basal metabolism determinations. In determining the blood volume per square meter of body surface a curve

TABLE 3

Iron requirements for growth: Males

AGE	WEIGHT	SURFACE AREA	B. V.	TOTAL B. V.	"NORMAL" Hg	TOTAL CIRCULATING Hg	TOTAL CIRCULATING Fe	ANNUAL GAIN, CIRCULATING Fe	ANNUAL GAIN, EXTRA-CIRCULATING Fe	TOTAL ANNUAL REQUIREMENT OF Fe
years	*kgm.*	*sq. m.*	*ml. per sq. m.*	*cc.*	*grams per 100 cc.*	*grams*	*grams*	*grams*	*grams*	*grams*
Birth	3.4	0.226	1,150	260	19.46	50.6	0.172	0.158	0.037	0.195
1	10.9	0.521	1,570	818	11.87	97.1	0.330	0.099	0.013	0.112
2	13.4	0.598	1,700	1,017	12.42	126.3	0.429	0.071	0.009	0.080
3	15.3	0.665	1,780	1,184	12.42	147.1	0.500	0.082	0.010	0.092
4	17.3	0.749	1,840	1,378	12.42	171.1	0.582	0.086	0.012	0.098
5	19.6	0.816	1,900	1,550	12.68	196.5	0.668	0.066	0.013	0.079
6	22.2	0.884	1,900	1,680	12.85	215.9	0.734	0.068	0.012	0.080
7	24.6	0.948	1,900	1,801	13.11	236.1	0.802	0.054	0.016	0.070
8	27.9	1.011	1,900	1,921	13.11	251.8	0.856	0.057	0.015	0.072
9	30.9	1.078	1,950	2,048	13.11	268.5	0.913	0.134	0.018	0.152
10	34.5	1.168	2,010	2,348	13.11	307.8	1.047	0.114	0.016	0.130
11	37.6	1.240	2,100	2,604	13.11	341.4	1.161	0.122	0.015	0.137
12	40.7	1.308	2,200	2,878	13.11	377.3	1.283	0.168	0.021	0.189
13	44.8	1.403	2,320	3,255	13.11	426.7	1.451	0.176	0.022	0.198
14	49.3	1.502	2,430	3,650	13.11	478.5	1.627	0.280	0.034	0.314
15	56.0	1.621	2,550	4,134	13.57	561.0	1.907	0.290	0.023	0.313
16	60.6	1.706	2,700	4,606	14.03	646.2	2.197	0.335	0.018	0.353
17	64.3	1.772	2,900	5,139	14.49	744.6	2.532	0.174	0.009	0.183
18	66.1	1.801	3,050	5,493	14.49	795.9	2.706	0.143	0.006	0.149
19	67.2	1.813	3,190	5,783	14.49	838.0	2.849	0.081	0	0.081
20	67.2	1.813	3,280	5,947	14.49	861.7	2.930	0.071	0	0.071
21		1.813	3,360	6,092	14.49	882.7	3.001	0.071	0	0
22		1.813	3,360	6,092	14.49	882.7	3.001	0.071	0	0
23		1.813	3,360	6,092	14.49	882.7	3.001			
Total requirement: Birth to 21 years										3.148

was constructed based upon the findings of Darrow, Soule and Buckman (43) from infancy through eleven years of age and the figure of

TABLE 4

Iron requirements for growth, menstruation and pregnancy: females

AGE	WEIGHT	SURFACE AREA	B. V.	TOTAL B. V.	"NORMAL" Hg	TOTAL CIRCULATING Hg	TOTAL CIRCULATING Fe	ANNUAL GAIN, CIRCULATING Fe	ANNUAL GAIN, EXTRA-CIRCULATING Fe	ANNUAL LOSS Fe BY CATAMENIA	TOTAL ANNUAL REQUIREMENT OF Fe
years	*kgm.*	*sq. m.*	*ml. per sq. m.*	*cc.*	*grams per 100 cc.*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*
Birth	3.26	0.222	1,150	255	19.46	49.6	0.169	0.148	0.034	0	0.182
1	10.2	0.500	1,570	785	11.87	93.2	0.317	0.100	0.012	0	0.112
2	12.5	0.581	1,700	988	12.42	122.7	0.417	0.079	0.013	0	0.092
3	15.1	0.660	1,780	1,175	12.42	145.9	0.496	0.068	0.012	0	0.080
4	17.4	0.726	1,840	1,336	12.42	165.9	0.564	0.077	0.010	0	0.087
5	19.5	0.782	1,900	1,486	12.68	188.4	0.641	0.091	0.015	0	0.106
6	22.4	0.882	1,900	1,676	12.85	215.4	0.732	0.065	0.013	0	0.078
7	25.1	0.941	1,900	1,788	13.11	234.4	0.797	0.053	0.014	0	0.067
8	27.9	1.004	1,900	1,908	13.11	250.1	0.850	0.088	0.020	0	0.108
9	31.8	1.079	1,950	2,104	13.11	275.8	0.938	0.103	0.017	0	0.120
10	35.2	1.162	2,010	2,336	13.11	306.2	1.041	0.143	0.020	0	0.163
11	39.2	1.265	2,100	2,657	13.11	348.3	1.184	0.142	0.022	0	0.164
12	43.7	1.352	2,200	2,974	13.11	389.9	1.326	0.171	0.021	0	0.192
13	47.9	1.448	2,320	3,359	13.11	440.4	1.497	0.131	0.014	0	0.145
14	50.7	1.503	2,430	3,652	13.11	478.8	1.628	0.151	0.019	0.298	0.468
15	54.5	1.565	2,550	3,991	13.11	523.2	1.779	0.120	0.006	0.298	0.424
16	55.7	1.578	2,700	4,261	13.11	558.6	1.899	0.193	0.007	0.298	0.498
17	57.0	1.601	2,900	4,643	13.25	615.2	2.092	0.135	0.002	0.298	0.435
18	57.4	1.605	3,050	4,895	13.38	655.0	2.227	0.150	0.004	0.298	0.452
19	58.2	1.621	3,190	5,171	13.52	699.1	2.377	0.067	0	0.298	0.365
20		1.621	3,280	5,317	13.52	718.9	2.444	0.060	0	0.298	0.358
21		1.621	3,360	5,447	13.52	736.4	2.504	0	0	0.298	0.298
22		1.621	3,360	5,447	13.52	736.4	2.504	0	0	0.298	0.298
23		1.621	3,360	5,447	13.52	736.4	2.504	0	0	0.298	0.298
24		1.621	3,360	5,447	13.52	736.4	2.504	0.374*	0	0	0.374
25		1.621	3,360	5,447	13.52	736.4	2.504	0	0	0.298	0.298
26		1.621	3,360	5,447	13.52	736.4	2.503				
Total requirement: Birth to 47 years											12.222

* Iron requirement for pregnancy (see text).

Brown and Roth (26) for adults (3360 cc. per square meter). Growth of body surface was assumed to cease at 21 years. This curve indicated a rapid gain of blood volume per sq. meter of body surface during the first 2 years of life, a slower gain to an almost stationary value at 9 years, then a fairly rapid rise to adult life. Some difficulty was experienced in adopting a figure for the new-born. The average figure of Lucas and Dearing (124) of 154 cc. per kilogram for infants 26 to 50 hours old seemed very high and gave figures for total circulating iron entirely out of proportion with modern experience. The figure 1150 cc. per square meter was finally chosen, and was obtained simply by carrying out the line upon the constructed chart to its logical conclusion. It was felt that this figure might give a somewhat low value for circulatory iron at birth but was more in keeping with experience. This figure is approximately the same as that given by Josephs (105),

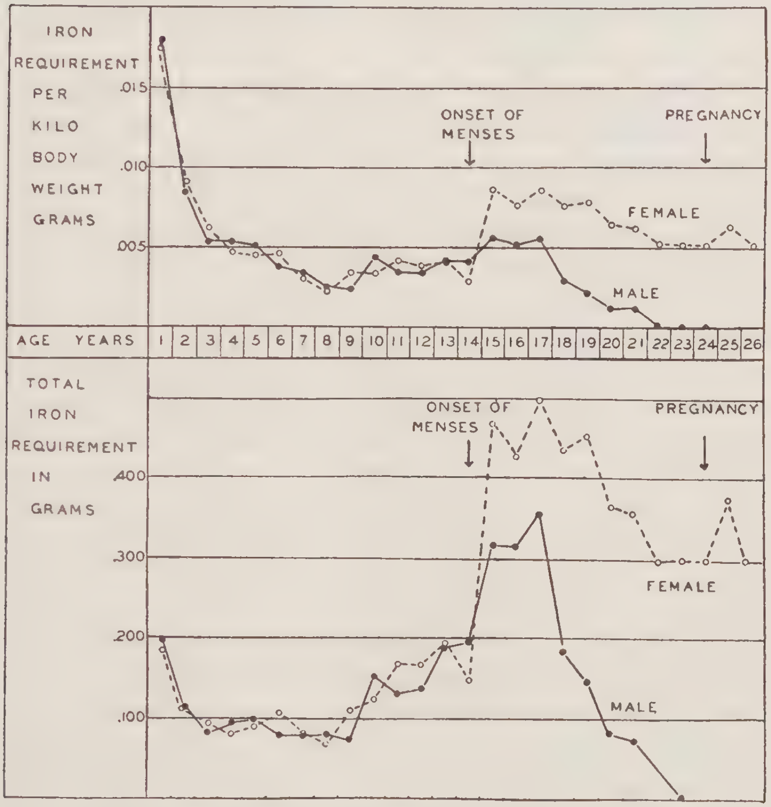

FIG. 1. ANNUAL IRON REQUIREMENTS OF MALES AND FEMALES

who calculated it on the assumption that the blood constitutes 7.6 per cent of the body weight.

The hemoglobin of the new-born was taken as 19.46 grams per 100 cc. from MacKay's figures for babies weighing 7 to 8 pounds (131). The hemoglobin standards from one year on were adopted from the arbitrary standards employed by Davidson, Fullerton and Campbell (45), the figure 11.87 grams per 100 cc. being the average of MacKay's figures for iron-fed infants.

The annual gain of extra-circulatory iron, or unavailable tissue iron was calculated from the arbitrary standard of 5 mgm. of iron per kilogram of body weight (105).

Catamenia was assumed to begin at 14 years and to cease at 47 years (74). A loss of 0.0229 grams of iron at each catamenia, representing a loss of about 50 cc. of blood, was the average of the determination in 4 subjects by Hoppe-Seyler (99) and 3 subjects by Ohlsen and Daum (159). Since this standard was adopted, Leverton and Roberts work (119) on 4 normal women has been published and shows an average blood loss of about 33 cc. for each period. There were assumed to be 13 periods in a year. No loss by catamenia was assumed during the year of pregnancy.

Quite arbitrarily, the loss of iron in pregnancy and at parturition was assumed to be twice the iron content of the fetus, or at least 0.374 grams. This would make a loss of about 350 cc. of blood at parturition which would include the iron content of the placenta. If, however, the iron content of the average new-born fetus is 0.375 grams, which is the value published by the White House Conference on Child Health and Protection (214) based on rather old figures, the iron requirement during pregnancy may be considerably higher, perhaps as much as 0.600 grams.

The iron loss by lactation has not been included in table 3. If, from the analyses of the Rowett Research Institute,[1] the average amount of iron in human milk is 0.17 mgm. per 100 cc., and the average daily quantity is, to give a round figure, 500 cc., a woman nursing her child would have a potential loss of 0.85 mgm. per day, or about 310 mgm. in one year. The amount of iron lost in a year by lactation is therefore apparently comparable to the amount lost in a year by menstruation.

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[1] Quoted from Davidson and Leitch (46) who give figures also of other authors which show considerable variation in the amount of iron in human milk.

A somewhat similar analysis of the growth requirement for iron has been reported by the White House Conference on Child Health and Protection (214). The figures in that report are somewhat higher than those here given, being based upon the total iron content of the body.

It is logical to assume that at the times during life in which the iron requirements are greatest, the drains upon the iron stores will be greatest and the possibility of iron deficiency occurring at these times will be greatest. The sum of all of the annual requirements for iron in the two sexes shows for females about four times the requirements for males, that is, about 12 grams for the former, about 3 grams for the latter. In infancy and childhood the requirements for the two sexes are equal. In childhood a relatively small annual iron requirement for growth will have more significance than the same requirement in the adult. For example, an annual requirement of 0.2 grams for a child weighing 11 kgm. could be considered equivalent to an annual requirement of 1.2 grams in an adult weighing 66 kgm. in its influence upon the hemoglobin iron and the reserve stores of iron in the body. This is illustrated in figure 1. The iron requirements in girlhood, at a time when both growth and menstruation are present, are great, and actually appear to be greater than the requirements for pregnancy itself. The sum of the annual requirements is greatest in females, of course, before the menopause. The assumption can be made, therefore, that *iron deficiency anemia in the absence of pathological blood loss is most likely to appear:* (*1*) *in childhood and at this time equally in the two sexes;* (*2*) *in adults more commonly in females than in males;* (*3*) *at the time of puberty particularly in females;* (*4*) *during pregnancy; and* (*5*) *in females late in menstrual life or at the time of the menopause.* Iron deficiency arising in adult males or in females after the menopause would seem almost certainly to be the result only of pathological blood loss. Clinical observation shows this assumption to be correct as will be demonstrated in the subsequent sections.

GENERAL CONSIDERATIONS OF ANEMIA OF IRON DEFICIENCY

I. Etiology

So far as the authors are aware, iron deficiency has never been produced in man or experimental animals by diets containing reduced amounts of iron unless other factors are brought into play, such as growth, pregnancy or bleeding. Iron, therefore, can perhaps be contrasted with certain other necessary elements of the body, such as calcium and nitrogen, the withdrawal of which from the food without other factors presumably will produce harmful deficiency states (although deficiency of these elements may even more readily occur if growth is present). The loss of iron by exogenous metabolism must be extremely small and of relative unimportance in the maintenance of the normal physiological state. Certainly any such loss is far exceeded by the loss of iron in the menses, in the growing child by the requirements for increasing total circulating hemoglobin, and in the pregnant woman by the requirements of the fetus. The work upon the iron balance in growing children, in pregnancy and in adult life, as is presented in table 2, is in accord with the theoretical requirements at these periods of life, as is illustrated in tables 3 and 4.

The normal human body contains latent stores of iron which can be called into use for emergency. An estimation of the normal daily requirement of iron should take into account the iron required for building these stores, and not alone the minimal requirements which have been considered in tables 3 and 4. Without these stores, an individual who had serious blood loss would remain anemic and in an in an iron deficient state for a prolonged period of time. In order to gain 1 per cent of hemoglobin the individual would have to retain about 25 mgm. of iron. Clinical experience has shown that under these circumstances a "normal" diet is inadequate in building hemoglobin, and that such individuals require medicinal iron. (If 50 per cent of the iron in a "normal" diet is absorbed, 3 or 4 days would be required to build only 1 per cent of hemoglobin.) The iron stores may therefore be considered as having a "buffer" action in the face of hemorrhage. They assist the individual to regain rapidly his normal level of hemoglobin after serious blood loss. They may eventually be built up again after months or years of an adequate dietary intake of iron while the individual has long since ceased to be anemic. If the stores have become exhausted by long continued bleeding, and if additional hemorrhage occurs, the individual will remain anemic for an indefinitely long period of time, particularly when gastro-intestinal abnormality interferes with the absorption of iron.

When blood loss occurs in the presence of sepsis or other states, regeneration of hemoglobin will take place at a much slower rate than normally or not at all, although supposedly available iron is present in the body. Much of the misconception in practice regarding iron deficiency and iron therapy is due to the non-recognition of the frequent complication of iron deficiency with other diseases. Infections, such as tuberculosis, typhoid fever, rheumatic fever and chronic pyogenic states, nephritis, severe liver disease and possibly cancer, not only are conducive to anemia themselves but will inhibit the utilization of inorganic iron salts.

Iron deficiency occurs when the demand for iron is greater than the supply of iron to the body. The various ways in which this may be brought about will be taken up in the consideration of the various types of iron deficiency.

II. Distribution, age and sex

Growth, blood loss, pregnancy, restricted diet, and gastro-intestinal disorders interfering with absorption are the factors which are responsible for iron deficiency. They may be present in any section of the world, and therefore there can be no purely geographical distribution of iron deficiency. There are, however, certain environmental factors which render some forms of iron deficiency more common in certain locations. The anemia associated with hookworm infection is primarily an anemia of iron deficiency resulting from intestinal bleeding, and is found in tropical and sub-tropical climates. It appears from the reports in the literature that "idiopathic" hypochromic anemia, an anemia of iron deficiency occurring in middle-aged women, who have defects of gastric secretion, is more common in northern Europe and in Canada and America than in other parts of the world. Customs which restrict the activities of women, such as those of certain sects of India, interfere with the appetite and with the intake of food iron so that at times when the demand for iron is increased, as in pregnancy, iron deficiency will develop. Local factors which interfere with the normal diet, such as war, epidemic and famine, may be conducive to iron deficiency along with other deficiency states. A study by Werdinius (210) is illustrative of the influence of a local peculiarity of diet upon the hemoglobin. He found a smaller average amount of the hemoglobin and a higher incidence of anemia in adults of northern Sweden, where the diet consisted mostly of milk and cereals, than in adults of southern Sweden who subsisted upon a mixed diet. Achlorhydria and intestinal disorders were more common in the population which subsisted upon the milk and cereal diet.

Among the anemias which may occur in man, generally speaking, the anemia of iron deficiency stands second possibly only to one: the anemia which follows or accompanies infectious disease. It is undoubtedly much more common than the remaining anemias such as the anemia which occurs in nephritis, leukemia, pernicious anemia and related macrocytic anemias. Although it is most commonly found in children, girls and adult women, it is certainly frequently seen in adult men in hospital wards who have suffered from blood loss. Excluding all cases resulting from uterine bleeding of various sorts, iron deficiency is more common among men than among women in the medical wards of the Boston City Hospital.

It is very difficult to estimate the incidence of iron deficiency in any community. Mild forms may escape detection except by painstaking and elaborate study. Indeed, we have no complete assurance that iron deficiency may not exist in the presence of a normal hemoglobin percentage, although this must be of relatively rare occurrence. Iron deficiency is not infrequently an accompaniment of other anemias and may modify or be modified by a coexisting anemia. Of 1168 women patients admitted to two wards in the Boston City Hospital in 1932, 37 per cent were found to have a reduced hemoglobin; of 1235 women patients admitted to the medical wards of a clinic in Leipzig, Germany, in the same year, 23 per cent were found to have a reduced hemoglobin (91). It is reasonable to suppose that at least one-half of these patients were deficient in iron, and that in the communities at large the incidence of anemia in the public hospital class was only somewhat less. In Scotland and England where the anemia of iron deficiency is relatively common among the children and women of the poor class certain statistics are available. Davidson, Fullerton and Campbell (45) reported observations upon the hemoglobin levels of 3500 individuals who belonged to the poorest classes in the Northeast of Scotland. Anemia, which was believed to be iron deficiency anemia, was found to be present in 41 per cent of infants under 2 years, 32 per cent of preschool children, 2 per cent of school children, 16 per cent of adolescent women, and 45 per cent of adult women. Anemia was absent in adolescent and adult males, except in association with organic disease. MacKay (132, 129) reported that more than two-thirds of the women of hospital class in London could be considered anemic, and that about 50 per cent of infants of the same class were anemic. She considered the anemia in these individuals to be due to an iron deficiency.

III. Factors other than iron influencing hemoglobin formation

The formation of hemoglobin can not take place in the absence of available iron. Nevertheless, there is no question that a large number of substances other than iron are involved, either directly or indirectly, in the formation of hemoglobin. Moreover, hemoglobin manufacture is a complicated chemical process related undoubtedly to other chemical processes of the body and modified by the general state of the body health.

Whipple, Robscheit-Robbins, and Walden (213) have shown that a particular liver extract prepared by precipitating the aqueous extract with 70 per cent alcohol has produced hemoglobin regeneration in dogs rendered chronically anemic by repeated bleeding and maintained on diets poor in hemoglobin-regeneration factors. This liver extract is ineffective in pernicious anemia. In human cases of hypochromic anemia its influence has not been satisfactorily demonstrated, although small responses of the blood have sometimes been shown. Rhodes, Castle, Payne and Lawson (177) have considered that the iron content of this liver extract might, in some part, account for the responses which have been shown. Extract of liver soluble in 70 per cent alcohol, which is effective in pernicious anemia, is without effect in hypochromic anemia. Cases occur, however, in which there is a deficiency of both iron and the substance active in pernicious anemia. In these cases such a type of liver extract will be effective to a certain extent. It is possible that when liver extract soluble in 70 per cent alcohol is given parenterally along with iron medication by mouth to cases of uncomplicated iron deficiency, regeneration of the blood may be somewhat greater than with iron alone (153). Raw liver and certain crude liver extracts may have an influence upon blood formation in iron deficiency of man (154, 110, 32, 177), particularly in cases of iron deficiency following blood loss in which normal amounts of hydrochloric acid are present in the gastric contents. In these clinical instances it is difficult to separate the influence of the iron content of the liver from that of the organic content upon the promotion of blood formation. Whereas raw liver and liver extracts may be helpful in assisting the regeneration of the blood in certain cases of hypochromic anemia, experience has not shown that they are of practical value or that they may take the place of adequate iron therapy.

There are a number of substances which, in the presence of iron, have been shown to have an additive effect upon hemoglobin production. Bile pigment, chlorophyll, and chlorophyll derivatives are effective, when added to small doses of iron, in increasing blood regeneration in hypochromic anemia of man (166, 164). Copper is apparently a necessary substance for hemoglobin formation and has been definitely proven to be such in small animals (53, 55). Other metals, such as arsenic, zinc, nickel, and manganese in very minute amounts, perhaps have a similar influence to copper (155). A peculiar relationship exists between calcium and iron (160). There is evidence to show that the retention of the iron from the food is favored when the calcium content of the food is high (186). The practical value of administering these substances in human hypochromic anemia is very doubtful. Copper and other minerals are present in the food of a varied diet and are also contaminants of the usual therapeutic preparations of inorganic iron. An anemia of cattle and sheep, which graze upon land the soil of which is apparently poor in certain minerals, has been investigated in Australia by Filmer and Underwood (61, 62, 202). A similar disease is apparently wide-spread throughout different sections of the world. The anemia in Australia is alleviated by crude iron compounds (limonite) but is not due to iron deficiency. Cobalt appears to be the specific element which is deficient. Man, in contrast to these animals, has extremely varied food and takes it from widely different geographical locations. It is extremely unlikely, therefore, that specific deficiencies of minerals other than iron which are required by the body in minute amounts will develop in man.

TYPES OF IRON DEFICIENCY ANEMIA AND SPECIAL FEATURES IN THEIR ETIOLOGY

The symptoms of iron deficiency anemia are similar to those of other kinds of anemia. Symptoms may be almost completely absent in children but may be very numerous and lead to great discomfort in chronic iron deficiency in adults. Weakness, easy fatigability, dyspnoea on exertion, palpitation, anorexia, and digestive disturbances together with other symptoms due to anemia per se are common. Symptoms particularly associated with different types of iron deficiency will be discussed in detail in the following sections.

Reimann (173) has grouped together the anemias in which there is a disturbance of hemoglobin formation and which are influenced by iron, calling them "ferrosensible chronische Chloranämien." He believed them to be the result of an iron deficiency just as clearly as other clinical states may be the result of a vitamin or other deficiency, and preferred to speak of them as "Asiderosen". With this point of view the authors heartily agree. A case of iron deficiency anemia is usually easily grouped under one of the following types which will be discussed:

I. Hypochromic anemia of infancy and childhood
II. Chlorosis
III. Hypochromic anemia of blood loss
IV. Hypochromic anemia of pregnancy
V. "Idiopathic" hypochromic anemia

I. Hypochromic anemia of infancy and childhood

Hypochromic anemia occurring after about the fourth month of infancy and in childhood has been referred to in the literature as "nutritional," "alimentary," or "chlorotic" anemia of infancy (95, 9, 205, 128, 189, 163). The diet usually is found to be reduced in iron, for example, when the infant is fed entirely upon cow's milk during the first year or when the appetite is interfered with by the presence of infection. The anemia responds readily to iron therapy. It is prevalent equally in the two sexes.

Responsible for the etiology of this anemia are, first, an increased demand for iron, and, secondly, a diminished supply of iron. Rapid growth produces an increased demand for iron. During the first year of life the total blood volume is approximately tripled and the total circulating hemoglobin is approximately doubled (see tables 3 and 4). Growth is relatively much more rapid during the first year of life than subsequently. Figuratively speaking, the infant bleeds into his own increasing blood volume.

A diminution of the supply of iron may be brought about in a number of different ways. If the mother is deficient in iron she may endow her infant with an insufficient supply of iron. If the infant is premature or is of low birth weight, as occurs in twins, its store of iron may be deficient. During the latter few months of pregnancy iron stores are laid down by the fetus, and if this storage period is interrupted the infant will begin life inadequately endowed with iron. Milk contains relatively small amounts of iron. If the milk feedings are not supplemented soon after dentition begins by iron-containing foods, such as meat, eggs and vegetables, the supply of iron may not be sufficient to meet the demand of growth. In the presence of infectious disease the appetite may be poor and the dietary iron may be reduced. It is possible that infectious disease may bring about a significant loss of iron from the body, that is, a negative iron balance, as the result of either a reduced intake of iron or this coupled with a somewhat increased output of iron because of tissue breakdown. Gastro-intestinal abnormalities such as diarrhoea may interfere with the absorption of iron and achlorhydria, which appears to be common in anemic children (80), can play its rôle in faulty absorption. It is possible for all these factors which have been considered to take place in one individual case. For example, an anemic mother, deficient in iron, may give birth to a premature infant which is fed on cow's milk exclusively, which usually contains less iron than human milk, and develops an infection at 4 months of age. One would not be surprised in such an infant to find a well-marked hypochromic anemia present at 8 months. If certain facts were known about this infant (the iron endowment at birth, the growth of the blood volume and the circulating hemoglobin, the iron content of the diet and of the excreta), a balance sheet could be drawn up which would show quantitatively just how the iron deficit was produced. Such a hypothetical case is illustrated in figure 2.

Josephs (105) has considered the relation of the iron metabolism and the iron stores to the possible production of nutritional anemia.

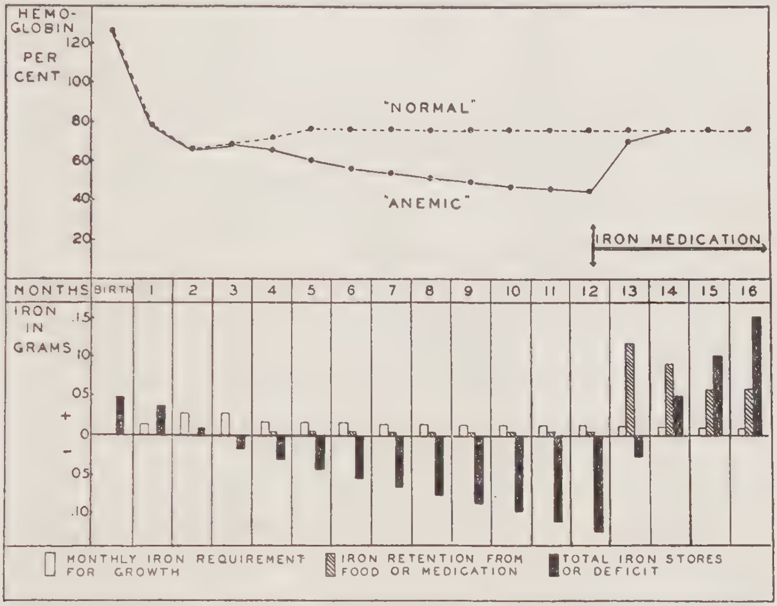

FIG. 2. HYPOTHETICAL CASE OF NUTRITIONAL ANEMIA OF CHILDHOOD

This chart shows the conditions which may lead to iron deficiency anemia in a child discovered at twelve months of age to have a hemoglobin of 44 per cent. Several assumptions are made: (1) that the iron stores (black columns) at birth are reduced either because of anemia in the mother or because of prematurity of the child; (2) that the retention of iron from the food (cross-hatched columns) is reduced, as may occur when the child is fed exclusively on cow's milk (about 0.1 mgm. iron per day retained). Since the monthly demand for iron for growth is not met by the diet, the iron stores are exhausted, an iron deficit and hence an anemia sets in. After the administration of iron the hemoglobin rises to normal and the iron stores are renewed.

He found positive iron balances after the second month of life. The iron stores seemed capable of lasting up to the sixth month. He concluded, on the basis of his calculations, that an exclusive milk diet can not bring about any great degree of anemia in infants, but that other factors causing a disturbance in iron metabolism must be present. It appears, therefore, that the healthy infant, normally endowed with iron at birth, is inherently capable of passing through the first year of life without developing iron deficiency even on an exclusive cow's milk diet which is relatively poor in iron. Josephs declared that further knowledge of iron metabolism was necessary before the etiology of hypochromic anemia in children could be explained. One can assume from his work that impoverishment of the three sources of supply of iron to the infant—the iron of the food, the iron stores and the iron contained in the excess hemoglobin found at birth, together with the demand for iron by growth, are possible factors in the production of iron deficiency. At least one other possible factor is brought out in his work: several of the children during the course of simple infections developed negative iron balances. A definite increase of iron output was not demonstrated during these infections, and a diminution of the iron intake at these times seemed mostly responsible for the negative iron balances. In general, Josephs (107) takes issue with the conception of iron deficiency as a clear clinical entity, believing that many factors are responsible for inadequate hemoglobin formation when hypochromic anemia is present.

Lintzel and Radeff (122) have compared the iron endowments and sources of iron supply of the young of different animals. There are animals like the rat, dog and pig in which suckling is prolonged and the iron of the mother's milk is important in preventing deficiency of iron, whereas there are others like the goat, rabbit and guinea pig which eat foreign food shortly after birth and in which milk iron has no importance. Man apparently is in an intermediate position; he has a moderate iron reserve at birth, a moderate hemoglobin reserve, takes some iron from the mother's milk and only later takes food other than milk.

Strauss (195) showed that there was no significant difference between the per cent of hemoglobin at birth of infants born of anemic mothers and that of infants born of non-anemic mothers, but that moderate to severe degrees of anemia developed in the former infants during the first year of life. This anemia was not present in infants born of mothers receiving iron during pregnancy. He believed that this form of anemia was "due to deficient storage of iron by the fetus dependent upon a deficient supply of this element in the mother."

MacKay (132) took the view that the iron-deficiency anemia displayed by mothers was related to the anemia of babies between 6 and 12 months of age of the same social class, that is, the anemia of babies was associated with a poor iron store at birth. The hemoglobin level of artificially fed infants was apt to be lower than that of breast fed infants (130). Statistical analysis of her figures showed that from 6 to 12 months of age the hemoglobin level correlated with the rate of growth (131). Rapid growth was considered an important factor in the development of "nutritional" anemia.

The hypochromic anemia of infants which is due to iron deficiency and occurs usually not earlier than the fourth month of life, must not be confused with the physiological fall of hemoglobin which commences immediately after birth and proceeds until the second or third month of life. The latter is believed to be due to an increased destruction of red cells and to be associated with the decreased need for circulating hemoglobin in the presence of a greater oxygen supply in extrauterine life (131, 107). The physiological fall of hemoglobin is greater the smaller the birth weight of the infant. In premature infants at the third month the hemoglobin may be so low that it is usually regarded as pathological. This has been termed the "anemia of premature infants." Whatever the cause of this anemia it is not the result of iron deficiency. The blood is not markedly hypochromic and there is no definite response to iron medication (180, 1, 131, 133, 106). After the fourth month of life premature infants may develop a hypochromic blood picture and the hemoglobin will respond in these circumstances to the administration of iron. The giving of iron to the premature infant early in life as a prophylactic measure is indicated and may prevent the appearance of hypochromic anemia or iron deficiency subsequently (137).

II. Chlorosis

Chlorosis may be defined as an iron deficiency anemia occurring in adolescent girls. Of all the types of iron deficiency it is the one which was earliest recognized as a clinical entity. A classic account was given by Johannes Lange in 1554 "De Morbo Virgineo" (115). Sydenham (1661) and Willis (1681) described the efficacy of iron in chlorosis. Ashwell's account in 1836 (6) corresponded to the descriptions of the disease in the nineteenth century. It was regarded as an "idiopathic" anemia, and, although it was extremely common, many vague opinions were expressed as to its nature and causation. As an example of this, a portion of the description by Osler in 1885 (162) is as follows:

> Chlorosis is a special form of anaemia distinguished by certain etiological and anatomical peculiarities. In the first place, it is a disease of the female sex; cases in the male are of extreme rarity. In the majority of instances it is associated with disturbed menstrual function or with the evolution of the reproductive organs at the period of puberty. Occasionally it occurs in pregnant women and in children. It is a common disease among the ill-fed, overworked young girls in large towns who are confined all day in close, badly-lighted rooms or who have to do much stair-climbing. Girls of the better classes are by no means exempt; indeed, some writers speak of it as specially prone to affect the higher ranks of life. Lack of proper exercise, good food, and fresh air, the mental stimulation of unhealthy literature, and masturbation are important factors. Emotional and nervous symptoms may be prominent—so much so that the disease is regarded by some as a neurosis. . . . The complexion is most peculiar, neither the blanched aspect of hemorrhage nor the muddy color of grave anaemia; but there is a curious yellow-green tinge in marked cases which has given the name to the disease (χλωρὸς), and also its popular designation, the green sickness.

Thus the disease was enshrouded in mystery. There was even some confusion as to the exact boundaries of chlorosis, whether or not the term should apply to iron-responding anemia at other ages or in the male sex. It is little wonder that today, when the disease is relatively uncommon and is so little recognized, it is regarded as a mysterious disease which has disappeared in the past.

Sound but little appreciated work upon chlorosis and iron in general was published by Stockman in 1893 to 1895 (191, 193, 194, 192)—work which seems to be chronologically out of order in the nineteenth century. Stockman believed that all other factors in the etiology of chlorosis were subservient to two great and direct causes, "namely, blood loss and insufficient supply of iron by the food." In his analysis of 3 cases he found the iron intake to average between 1.3 and 3.2 mgm. daily. "Whereas the menses may not be excessive, such a loss was relatively great and poorly sustained when the intake was deficient in iron...Further, girls develop with extreme rapidity from 15 to 18, throwing a great strain on the organism, which suffers in various ways besides in blood forming." His cases of chlorosis ranged in age from 13 to 35 years, the average being about 20 years.

Davidson and Leitch in their monograph on "The Nutritional Anaemias" (46) have made some valuable comments upon the causation of chlorosis and the reasons for its relative disappearance:

> Although described as a primary anaemia in all textbooks of medicine, there can be little doubt that chlorosis was essentially a nutritional anaemia, consequent on deficient iron intake.... A mild degree of hypochromic anaemia is apt to occur at puberty, but when growth slows down the iron intake of the diet is usually sufficient to produce a cure. Changes in environment and habits, the achievement by working women of better hygiene conditions, including higher wages, and the dissemination of knowledge regarding the importance of diet in relation to health, have banished a serious form of anaemia which caused an enormous degree of incapacity and economic inefficiency.

Tables 3 and 4 and figure 1 illustrate the increased requirements of iron during the adolescent years. In girls there is an acceleration of growth after 9 years of age, and an accompanying increase of blood volume and total circulating hemoglobin. The occurrence of menstruation at 14 years produces the additional demand for iron, which if not met by the iron reserves or the iron of the diet results in the appearance of anemia. The girl after puberty is subjected to circumstances which may result in iron deficiency. Figure 3 illustrates hypothetically the quantitative changes of iron metabolism resulting in the appearance of hypochromic anemia in a girl having a poor iron store at puberty and partaking of a diet low in iron. If no iron deficiency has been present in infancy and childhood, if the reserves of iron are large at the time of puberty, and if the appetite is good and the dietary intake rich in iron, the excessive demands for iron will be met and the adolescent years will be passed without the appearance of a hypochromic anemia. Various factors or combinations of circumstances in addition to the normally increased demands for iron by growth and menstruation can produce iron deficiency at this time of life. The iron reserves may be poor at puberty owing to an inadequate endowment of iron at birth from an anemic mother, and an inadequate diet during pre-school and school years. Under these circumstances hypochromic anemia may not appear until the additional demand for iron during adolescent years occurs. Simply an inadequate diet, or an inadequate absorption of iron due to gastro-intestinal abnormalities may thus lead to a hypochromic anemia. Repeated or prolonged infections may be a factor in reducing the dietary intake of iron. Menorrhagia or blood loss from epistaxis or gastro-intestinal bleeding may be an additional factor which brings about a hypochromic anemia. Combinations of these are common.

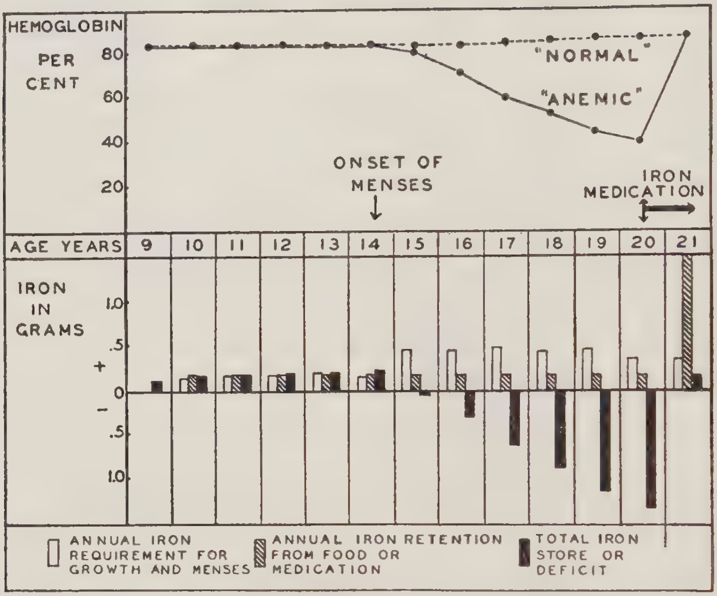

FIG. 3. HYPOTHETICAL CASE OF CHLOROSIS

The chart illustrates the conditions which may lead to iron deficiency anemia in a girl discovered at 20 years of age to have a hemoglobin of 40 per cent. It is assumed that the iron stores (black columns) up to the age of 14 years are small, although no anemia is present. It is also assumed that the diet is poor in iron or that a poor diet is combined with poor intestinal absorption of iron, so that the iron retention (crosshatched columns) is small. Menstruation is assumed to be normal (amounting to 50 cc. of blood per month or 300 mgm. of iron per year). When the increased requirement of iron (white columns) due to acceleration of growth and onset of menses occurs after puberty the amount of iron retained does not suffice. The iron store becomes a deficit and anemia results. When iron is administered the hemoglobin rises and iron is stored. The production of anemia, of course, may be accelerated or enhanced if there is increased blood loss such as menorrhagia or epistaxis.

Campbell (29) has commented upon the frequency of hematemesis and the occasional occurrence of hypochlorhydria in chlorosis. There is no question that more critical and exact modern methods of study have discovered in many cases of hypochromic anemia in girls direct sources of blood loss. Exacting hematological methods and better understanding of blood diseases in general have more closely defined the field.

Since the cause of chlorosis depends upon conditions that are universally current, such as, growth, blood loss and inadequate diet, it is unlikely that the disease should completely disappear. It is the opinion of the authors that the disease has not disappeared but on the contrary in mild form is fairly common, and in the severe form not extremely rare. Moreover, there seems to be no definite evidence that chlorosis is essentially different from iron deficiency occurring at other ages. In the routine examination of 38 presumably healthy student nurses between the ages of 18 and 23 years, it was found that 26 per cent had a moderate anemia with a hemoglobin between 70 and 79 per cent.[2] Hypochromic anemia of severe grade and responding to iron has been fairly frequently discovered in adolescent girls who entered the hospital for treatment of some other disease such as pulmonary tuberculosis, pleurisy with effusion, lobar pneumonia, and pyelitis. Four striking cases of hypochromic anemia in girls which seemed to correspond to the older descriptions of chlorosis have been studied recently (165). The summary of one of these cases is as follows:

A 16-year-old girl complained of weakness. Her grandmother had been treated for anemia 20 years previously. In childhood the patient enjoyed robust health. Upon moving from the country to the city two years previously, the family lived in cramped lodgings. The patient's appetite failed and she developed a dislike particularly for meat and green vegetables (calculated average daily iron intake 5.4 mgm.). For several years moderate nosebleeds occurred on the average of once a month. For one year menstruation came at 3-week cycles with excessive flow for one week.

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[2] In this and in subsequent reports of hemoglobin percentage, 100 per cent was taken as the equivalent of 15.6 grams per 100 cc. of blood, or 20.9 volumes per cent oxygen capacity.

On examination she was thin, extremely pale and listless. The teeth were carious. The tongue was normal. There was a systolic murmur at the mitral valve area.

The urine and stools were normal. Gastric analysis yielded only a trace of free hydrochloric acid after histamine. The red blood cells were 2,370,000 per cubic millimeter; the hemoglobin was 29 per cent.

The blood responded well to iron medication. She feels well at present and has been able to take a normal diet. A normal blood level has been maintained for 4 months without iron therapy. Menstrual periods now appear at 28-day cycles with average flow.

The etiological factors in this case were: a probable poor iron endowment at birth; rapid growth; poor iron intake; hypochlorhydria; menorrhagia; epistaxis.

In at least 2 of the 4 patients the hereditary background seemed important, and in 3 of them the presence of reduced amounts of free acid in the stomach may have been a factor in limiting the intake of iron. Pathological blood loss was present in only two. Putting aside the factors of poor iron intake, and excessive blood loss at menstruation or by epistaxis, it is obvious that the largest drain on the iron stores of girls of this age is due to growth and menstruation. If the growth requirement from 14 to 15 years is equivalent to 340 cc. of blood, and the average annual menstrual loss is 650 cc., the total annual "blood loss" is nearly 1000 cc., or about one-fourth of the total blood volume at this age.

Hypochromic anemia in 2 young girls who were sisters has also been reported by Heath (89). In one sister anemia was profound after hemetemesis from a peptic ulcer. In the other sister anemia was slight and seemed to depend upon growth, epistaxis, and the early onset of menses.

As a converse to the fact that the combination of growth and menstruation produces an excessive iron requirement at puberty, one may wonder why hypochromic anemia is not observed more commonly in adolescent girls. However, it can be argued that the excessive drain on the iron reserves can be met adequately when the diet is good and the appetite normal in hygienic surroundings. The normal conditions are as follows: a healthy mother (normal endowment of iron at birth); good diet from childhood on; normal and not too rapid growth; normal menstruation; absence of blood loss other than menstruation; absence of gastro-intestinal abnormality. In an anemic girl, if a careful history elicits no abnormality of these factors, the anemia is presumably not due to iron deficiency. A combination of the abnormal conditions will almost certainly be found when iron deficiency is present: anemic mother (poor endowment of iron at birth); diet poor in iron; rapid growth; meonorrhagia; bleeding other than menstrual; gastro-intestinal abnormality.

That there is a certain relationship between chlorosis and "idiopathic" hypochromic anemia occurring in middleaged women is indisputable. The exact relationship is impossible to define. It is apparently common for chlorotic girls to have anemic mothers, just as the hypochromic anemia of childhood may occur in children born of anemic mothers. It is not uncommon to obtain a history of anemia in girlhood in cases of "idiopathic" hypochromic anemia. Anemia in daughters of patients suffering from "idiopathic" hypochromic anemia, pernicious anemia, or both, have been reported (86). Witts (220) makes a sharp clinical distinction based upon the findings of gastric acidity in chlorosis and of achylia gastrica and glossitis in the older age group. Bloomfield (18), however, argues that such distinctions are unwarranted and arbitrary. The popular recognition of the syndrome of "idiopathic" hypochromic anemia following the decline of adolescent chlorosis might indicate perhaps a shift of hypochromic anemia in females during the last two decades towards a later age group.

Hypochromic anemia in adolescent males is relatively uncommon. The authors have not observed it except in the presence of excessive blood loss or marked gastro-intestinal abnormality. This is perhaps surprising because the requirements of iron for growth in boys are large and approach those for growth and menstruation in girls. It is probable that the greater freedom of boys in out-door activities, the greater muscular activity and, as a result of these, the greater intake of food make the difference. Minot (145) has observed hypochromic anemia in adolescent youths associated with very inadequate diets. Reynolds (175) states that he has observed a mild iron-responding anemia without blood loss in 2 adolescent schoolboys who grew rapidly. Witts (219) in 1930 reported hypochromic anemia without definite etiology in 5 males, ages 18 to 28 years. The diets of these men were not reported. Witts stated that "anaemia for which no cause can be found is very uncommon in men." He has since then emphasized this statement and has concluded that hypochromic anemia in adult men is very strong evidence that bleeding has taken place (222).

III. Hypochromic anemia of blood loss

Iron deficiency may follow blood loss from any source and at any age. To lose blood means, in a sense, to lose iron. At least four-fifths of the functioning iron of the body is located in the circulating hemoglobin and under normal circumstances the concentration of iron in the blood is much greater than that in any other organ of the body. The relatively large amount of iron in the blood is a fact which has been too easily forgotten in attempts to explain the etiology of certain forms of iron deficiency. In adult persons prolonged excessive loss of blood almost certainly will lead to iron deficiency. The presence of iron deficiency in adult man, as shown by a hypochromic anemia and the regeneration of hemoglobin with medication, is an almost certain sign that there has been excessive blood loss.

In table 5 is shown an analysis of 122 cases of iron deficiency in adults resulting from blood loss which were studied in this clinic. Certain criteria for iron deficiency were strictly adhered to: hypochromic anemia, a specific response of the blood to iron medication with increase of hemoglobin and characteristic response of reticulocytes. In only a few instances was the hemoglobin initially as high as 60 per cent. Cases with severe complications such as severe sepsis, nephritis and advanced neoplasm were excluded. The cases were carefully selected for investigative purposes but they illustrate most of the common sources of serious blood loss. Gastro-intestinal abnormality of one sort or another is the most common source of blood loss resulting in hypochromic anemia in a medical clinic. No cases of blood loss from wounds were studied. The group of "miscellaneous sources of blood loss" was made up mostly of cases having gastro-intestinal bleeding from various causes, such as carcinoma of the colon, ulcerative colitis, cirrhosis of the liver with esophageal varices, amebic dysentery and sarcoma of the duodenum.

There was also a case of bleeding from carcinoma of the bladder, one of familial teliangiectasia with chiefly epistaxis, and 2 cases in which, following dental extraction, bleeding occurred; one of these was a case of hemophilia. In 4 cases blood loss was not demonstrated but undoubtedly existed previous to observation and went unrecognized by the patient.

In table 6 are included the well-studied cases of "idiopathic" hypochromic anemia which were seen in this clinic. As will be discussed in the section on "idiopathic" hypochromic anemia, most if not all of these cases have excessive blood loss. It is true that in many of these cases the diet is low in iron and there is malabsorption from the gastro-intestinal tract associated with achlorhydria, but these factors are etiological only in the sense that iron is not available in large enough quantities to repair the deficiency produced by the iron losses. Therefore, it has seemed reasonable to consider the cases of "idiopathic" hypochromic anemia as a special form of the hypochromic anemia of blood loss.

TABLE 5

Hypochromic anemia of blood loss

Chief sources of blood loss and acidity of gastric contents. Number of cases

CHIEF SOURCE OF BLOOD LOSS	MALES			FEMALES			TOTAL		
	Total	Cases with acid	Cases without acid	Total	Cases with acid	Cases without acid	Total	Cases with acid	Cases without acid
Peptic ulcer	24	4	1	7	2	0	31	6	1
Carcinoma of stomach	20	3	9	2	0	1	22	3	10
Hemorrhoids	13	8	2	3	2	0	16	10	2
Menorrhagia and metrorrhagia				14	9	0	14	9	0
G. I. bleeding (source unknown)	7	3	2	1	0	0	8	3	2
Abortion, miscarriage or post-pregnancy bleeding				9	2	1	9	2	1
Epistaxis	4	1	0	1	0	0	5	1	0
Miscellaneous sources	4	0	1	9	1	3	13	1	4
Blood loss unidentified	3	0	2	1	1	0	4	1	2
Totals	75	19	17	47	17	5	122	36	22

In the entire group of 182 cases of hypochromic anemia of blood loss 59 per cent were women. It is noteworthy that if the cases having uterine bleeding from various causes are excluded, only 37 per cent were women. In the population at large there is no question that a slight degree of hypochromic anemia is much more common in women than in men, and is usually related to iron loss by menstruation, pregnancy and lactation.

Cases of acute blood loss during the acute phase are not included in this series. It is difficult to prophesy initially in individual cases of acute blood loss whether or not the condition will result in an iron deficiency because the characteristics of a hypochromic anemia do not appear until later. Usually several weeks must lapse after the hemorrhage before it is certain that the hemoglobin has reached a stable low value and a hypochromic anemia has resulted. There is usually a slight increase in mean corpuscular volume in normal persons shortly after any acute blood loss (85) (which later becomes microcytic if the iron reserves have been depleted). An adequate control period until the hemoglobin and the reticulocyte level become stable is exceedingly important in the study of all kinds of iron deficiency,

TABLE 6

Hypochromic anemia of blood loss including cases of "idiopathic" hypochromic anemia

Chief source of blood loss and acidity of stomach contents. Number of cases

CHIEF SOURCE OF BLOOD LOSS	MALES			FEMALES			TOTAL		
	Total	Cases with acid	Cases without acid	Total	Cases with acid	Cases without acid	Total	Cases with acid	Cases without acid
Peptic ulcer	24	4	1	7	2	0	31	6	1
Carcinoma of stomach	20	3	9	2	0	1	22	3	10
Hemorrhoids	13	8	2	10	3	6	23	11	8
Menorrhagia and metrorrhagia				51	16	29	51	16	29
G. I. bleeding (source unknown)	7	3	2	3	1	1	10	4	3
Abortion, miscarriage and post-pregnancy bleeding				13	5	2	13	5	2
Epistaxis	4	1	0	3	0	2	7	1	2
Miscellaneous sources	4	0	1	10	1	4	14	1	5
Blood loss unidentified	3	0	2	8	2	6	11	2	8
Total	75	19	17	107	30	51	182	49	68

particularly when it is desired to examine the effectiveness of iron medication (140, 84). It is a matter of clinical impression that iron deficiency results from acute blood loss particularly in those individuals who have had a diet reduced in iron. It is also the impression of the authors that diets reduced in iron as well as in other essential food factors such as protein are exceedingly common in persons suffering from hypochromic anemia of blood loss.

The number of cases with and without acid in the gastric contents are included in the tables under discussion. It is unfortunate that routine gastric analyses were not made in all cases. The figures serve to demonstrate that achlorhydria is common in the hypochromic anemia of blood loss. Whether or not iron deficiency and anemia are factors in the production of achlorhydria can not be decided at the present time.

Outstanding examples of iron-deficiency anemia arising in the main from gastro-intestinal bleeding are ankylostomiasis, bleeding varices and ulceration of different parts of the gastro-intestinal tract. Diaphragmatic hernia may be found to be the cause in cases of hypochromic anemia that at first appear to be of obscure origin (21). The anemia in Banti's disease can arise due to blood loss from ruptured esophageal varices as has been shown by Davidson (44). When such is the case, the anemia is hypochromic and responds readily to iron medication. The anemia in ankylostomiasis has been shown by various physicians (109, 177, 38, 65) to be alleviated by the administration of iron but not satisfactorily by the expulsion of the parasites. Although blood loss is undoubtedly the primary cause of the hypochromic anemia in ankylostomiasis additional factors in the etiology of the anemia are growth and poor iron endowment in children, iron-poor diets and probably disturbances in the gastro-intestinal absorptive mechanism.

IV. Hypochromic anemia of pregnancy

A moderate reduction of the hemoglobin percentage occurs normally in pregnancy. This is a "physiological anemia" and depends upon an increase in the total plasma volume of the blood. Consecutive blood studies during pregnancy show a steady reduction of the number of red blood cells and the percentage of hemoglobin until about the sixth month (199, 50). After the sixth month there is either no further change or a slight increase in the red blood cells and hemoglobin. Within about 2 weeks after pregnancy has terminated, the red blood cells and hemoglobin increase to values normal for non-pregnant women. The average reduction of the number of red blood cells is about 500,000 per cubic millimeter; of the hemoglobin, about 10 per cent.

This hydremia of pregnancy is not to be confused with the true anemias of pregnancy, the most common of which is hypochromic anemia from iron deficiency, less common, normocytic anemia and macrocytic anemia due to deficiency of the factor effective in pernicious anemia. Bland, Goldstein and First (15) found anemia in one-half of ward maternity patients, and in about one-quarter of private maternity patients. The demand for iron by the growing fetus is obvious and must be supplied either from the stores of iron in the mother or from her food. Since there are only about 500 mgm. of iron in the average fetus at term (less if the mother is deficient in iron), the loss of iron from the mother is not large and can probably not exceed 20 per cent of her hemoglobin. If a 10 per cent reduction of the hemoglobin because of the "physiological anemia," may be responsible for a hemoglobin level of about 70 per cent, a further reduction of 20 per cent due to the demands of the fetus for iron will result in a hemoglobin level of about 50 per cent. For this state of affairs the assumption would have to be made that the pregnant woman retained no iron from her food and that she entered pregnancy with no available iron stores. Hemoglobin levels below 50 per cent, when the hypochromic anemia of pregnancy is present, are not rare but without much question occur in those patients who have been anemic before pregnancy or who had blood loss during pregnancy. Fullerton (70) has considered that a reduction of the hemoglobin by only 10 per cent in addition to the physiological fall is possible, and that the conception that uncomplicated pregnancy frequently produces a severe degree of hypochromic anemia should be discarded. Bethel (13) essentially is in agreement with this.

Strauss and Castle (196, 199, 197) have shown the relationships between dietary deficiency, poor gastric secretion and malabsorption to blood formation during pregnancy. They showed that the secretion of hydrochloric acid and pepsin was commonly diminished during pregnancy particularly during the middle third of pregnancy. Anemia occurred only in those patients who had a prolonged defective dietary and gastric anacidity or related gastro-intestinal disturbances. They concluded that the hypochromic anemia of pregnancy was due essentially to three factors acting together: dietary deficiency, malabsorption from the gastro-intestinal tract, associated usually with diminution of the gastric acidity, and the demand by the fetus for blood-building materials. The anemia is relieved either during or after pregnancy by the administration of iron in suitable doses. They concede the possibility of all the conditions leading to other forms of anemia being present in the pregnant as in the non-pregnant. An analogy between hypochromic anemia of pregnancy and the much rarer pernicious anemia of pregnancy was brought out in their work. They demonstrated clearly that the intrinsic factor as well as hydrochloric acid and pepsin may be depressed during pregnancy.

Fullerton (70) discussed the quantitative aspects of the iron metabolism in pregnancy. Taking 550 mgm. as the total "iron demand" and 280 days as the duration of gestation, he assumed that a positive iron balance of 2 mgm. daily would be required to satisfy the requirements of the fetus, and that this can be supplied since it represents less than one-half of the available iron in the average diet of women of the poor classes. He admitted a possible retention of only 1 mgm. of iron daily in women with gastric hypofunction and an iron-poor diet, therefore, a possible loss of about 270 mgm. of iron from the mother's stores or from the circulating hemoglobin, amounting to a reduction of about 10 per cent of hemoglobin. Retention of iron during pregnancy has been shown, but the problem of iron metabolism in hypochromic anemia of pregnancy has not been studied. Indeed, much work must be done upon iron metabolism in hypochromic anemia in general before definite conclusions can be reached regarding the amount of iron available from the food.

It is certain that repeated and frequent pregnancies can condition chronic hypochromic anemia. Post-partum bleeding, although always present, is extremely variable, and may be excessive and productive of hypochromic anemia of blood loss. Repeated pregnancies, by increasing the demand for iron to supply the fetus, to supply the iron lost in post-partum bleeding and in lactation may gradually produce profound iron deficiency.

V. "Idiopathic" hypochromic anemia

(Simple achlorhydric anemia, simple achylic anemia, primary hypochromic anemia, achylic chloranemia, chronic chlorosis, chronic microcytic anemia, essential hypochromic anemia)

"Idiopathic" hypochromic anemia is rather difficult to define because it does not appear to be a very distinct clinical entity (18). In a narrow sense it may be defined as a chronic hypochromic anemia appearing usually in middle-aged women who have an absence or reduction of free hydrochloric acid in the stomach. Characteristically it presents a striking picture: the patient, a chronic invalid, weak, ambitionless, querulous, complains of dyspnoea and palpitation on exertion, flatulence and vague abdominal symptoms; feeling of cold and transient paraesthesias of the extremities. There is no icterus, the skin having a remarkably pale, waxy hue and the sclerae bluish, although the anemia may be more marked than the appearance of the patient indicates. The disease appears to be more common in blonde, nordic types, rare in negroes. The hair is usually gray or white. Certain ectodermal changes are common. The skin sometimes appears atrophic particularly over the hands, resembling the skin of the hands in rheumatoid (atrophic) arthritis; indeed, chronic iron deficiency is often present in rheumatoid arthritis. The hair may be dry and fine and come out easily by gentle pulling. The finger nails, rarely the toe nails, may be flattened or actually concave, thin, and brittle. The nail beds are sometimes the seat of a chronic infection. Fissures, or rhagades, at the corners of the mouth may be present, and the healing of these may leave small scars at the corners of the mouth with a tendency to making the orifice of the mouth smaller. A brownish, light pigmentation, particularly on the neck and upper thorax has occasionally been observed. Frequently there is a history of easy bruising, and ecchymoses are seen, more rarely petechiae. Almost complete atrophy of the tongue papillae especially at the tip and edges is common. The tongue is often smaller than normal as though the changes affected the musculature. The pharynx may appear small and the mucous membrane is often atrophic and somewhat dry in appearance. Examination by the gastroscope is said to reveal an atrophic condition of the stomach mucous membrane. The heart in severe cases may be somewhat enlarged on physical examination and when measured by x-ray (52). There are no significant electrocardiographic findings (52). A functional systolic murmur heard best along the left border of the sternum is practically the rule. Rarely a functional diastolic murmur may be heard in this region. Dependent edema is not uncommon in severe cases. Congestion of the lungs is less common. The lymph nodes are not enlarged. An enlargement of the thyroid gland without thyrotoxicosis has been observed in the authors' cases more commonly than can be accounted for by chance. The liver edge and the spleen are frequently palpable. There is achlorhydria or hypochlorhydria; the blood picture is that of a marked hypochromic anemia. The blood returns to normal with the administration of iron, and the signs and symptoms eventually disappear.

Writers in the last century in describing chlorosis in girls frequently referred to a form which appeared later in life. Faber (56, 57, 58) first called attention to the association of this type of anemia with achylia gastrica, although Fenwick (60) many years previously emphasized in general the relationship of the gastro-intestinal tract to the state of the blood. In recent years, during the revival of interest in anemia, many authors have described cases of the condition (2. 221, 125, 47, 40, 144, 208, 141, 183, 146, 83, 203, 217). It is to be noted that the names given to the disease imply either its association with achylia gastrica or that its etiology is unknown. Not infrequently dysphagia is present accompanied by atrophy of the pharyngeal mucous membrane and sometimes by a web formation at the pharyngeal-esophageal junction, a condition described first by Kelly and by Paterson (112, 167), and commonly referred to as the Plummer-Vinson Syndrome (206). Suzman (200) has recently given an excellent description of the disease.

In considering the etiology of "idiopathic" hypochromic anemia it must be emphasized that it is an anemia resulting from an iron deficiency and that the anemia can be relieved quantitatively, as shown by the fact that iron given parenterally appears almost entirely as circulating hemoglobin iron (93). The primary cause for the iron deficiency is a loss of iron through some route. This assertion is borne out in "idiopathic" hypochromic anemia by clinical observations which will be discussed subsequently. The accessory signs and symptoms such as the brittle nails, atrophy of the tongue, and changes probably widespread throughout the gastro-intestinal tract, and skin changes which are peculiar to the condition have not been proven to be the result of iron deficiency, although they disappear after iron medication. Associated but unknown deficient factors may be responsible for these changes. Probably in many cases there is a border-line state of deficiency of some of the known vitamins, such as vitamin A and B_2, and undoubtedly at times deficiency of protein and calcium produced by faulty diets. The edema may be accompanied by low plasma proteins. X-ray examination of the skeleton may reveal a diffuse decalcification.

In table 7 are given certain data concerning 60 cases of "idiopathic" hypochromic anemia studied in this clinic. These were selected from a somewhat larger group of similar cases because of the completeness of the observations. They include only female patients. Male patients who might be included in this group have almost invariably shown extensive blood loss. The average number of red blood cells was 3,540,000 per cubic millimeter. The average hemoglobin was 39.8 per cent. The color index was reduced in all, averaging 0.56 and varying from 0.3 to 0.8. Twenty-one cases had color indices of 0.5 or less. After a control period during which no rise of hemoglobin occurred, each of the cases responded to iron medication with an increase of the hemoglobin concentration and, in all cases in which daily reticulocyte counts were made, there was a characteristic response of these young cells.

The etiological factors considered in the table are, first, those concerning the supply of iron: the iron content of the diet and the acidity of the gastric juice; secondly, those concerning the loss of iron: the number of pregnancies and bleeding from various sources.

Anacidity after the injection of histamine was present in 45 cases or 75 per cent. Hypoacidity was present in the majority of the remainder. It is assumed that anacidity, although without doubt an important factor in inhibiting resorption of iron from the food, reflects a disorder of the absorptive mechanism of the gastro-intestinal

TABLE 7

Cases of "idiopathic" hypochromic anemia and their etiological factors

(X = present)

CASE NUMBER	AGE	INITIAL R.B.C.	INITIAL HEMOGLOBIN	ANACIDITY AFTER HISTAMINE	DIET POOR IN IRON	PREGNANCIES OVER 4	MENORRHAGIA	BLEEDING HEMORRHOIDS	EPISTAXIS	OTHER SOURCES OF BLOOD LOSS
		millions	*per cent*							
1	29	3.5	38	X	X	X	X			
2	47	3.6	45	X	X	X	X			
3	48	3.9	56	X			X			
4	36	3.6	48	X	X		X			
5	40	2.3	33	X				X	X	
6	40	3.3	54			X	X			
7	41	4.1	32	X		X		X		
8	33	3.7	41	X		X	X			
9	38	2.7	33	X	X		X			
10	41	3.6	42	X	X		X			
11	40	3.3	36	X	X		X			
12	37	2.9	32	X			X			
13	42	1.3	8	X	X			X		
14	41	2.5	39	X	X	X	X		X	
15	32	4.5	46	X		X	X		X	
16	41	1.6	14	X	X		X			
17	42	3.6	43	X		X	X			
18	49	4.7	50	X					X	
19	40	3.7	50		X	X				X
20	44	4.5	50	X	X	X	X			
21	35	4.6	48	X	X		X	X	X	
22	48	3.4	36	X			X			
23	45	3.3	31				X			
24	39	3.7	45	X		X	X		X	
25	36	4.6	57				X			
26	46	3.7	37	X			X			
27	53	4.9	42	X	X	X	X		X	X
28	35	5.1	63				X			
29	37	3.8	44	X	X	X	X	X		
30	29	2.7	35			X	X		X	
31	39	3.0	30	X	X	X	X			
32	39	3.7	47		X	X	X			
33	36	3.4	36	X	X	X	X			
34	34	4.8	56	X			X			
35	37	2.4	20	X		X	X			
36	53	3.9	52		X	X	X	X		
37	33	3.8	45	X	X	X	X			

TABLE 7—*Concluded*

CASE NUMBER	AGE	INITIAL R.B.C.	INITIAL HEMOGLOBIN	ANACIDITY AFTER HISTAMINE	DIET POOR IN IRON	PREGNANCIES OVER 4	MENORRHAGIA	BLEEDING HEMORRHOIDS	EPISTAXIS	OTHER SOURCES OF BLOOD LOSS
		millions	*per cent*							
38	62	1.9	16	X	X	X		X		
39	35	4.0	52	X	X	X	X	X		
40	61	3.3	35	X	X					X
41	44	3.9	54		X	X	X			
42	42	4.3	30		X		X			
43	23	3.4	41		X			X		X
44	43	2.6	21	X	X				X	
45	42	3.7	35	X		X	X	X		
46	50	2.7	29	X	X			X		X
47	44	4.6	40	X	X		X			
48	67	3.5	34		X			X		
49	38	3.4	50	X	X	X				X
50	48	2.7	41	X	X			X		
51	39	2.0	20		X	X				X
52	52	2.8	21	X	X	X		X		
53	36	3.6	32		X					X
54	42	4.9	57	X						
55	40	4.6	55	X						
56	32	3.6	34	X						
57	65	4.9	51	X						
58	33	2.8	31	X	X					
59	57	3.7	45	X	X					
60	40	4.1	51	X	X	X				
Average....	42	3.54	39.8							
Total........................				45	37	28	37	14	9	8

tract. The diet was definitely poor in iron-containing foods in 37 cases. Such diets usually contained a scarcity or absence of the following foods in order of frequency: meat and eggs, colored vegetables, fruit. Frequently there was a reduction in the total calories, but often for the lack of fresh, non-processed foods there were substituted concentrated carbohydrate foods, chiefly bread, potatoes and sugar. Bread, butter and tea were often the chief foods consumed. Even in the patients who partook almost exclusively of bread and tea, however, appreciable amounts of iron were contained in the diet;

bread, for example, being relatively rich in iron. In estimating the iron content of the diets of 44 patients, the authors found that it ranged from 4.3 to 14.4 mgm. of iron a day, and averaged 9.0 mgm. Diets exceedingly low in iron are very unpalatable indeed. Nevertheless, since the average daily requirements for the iron lost by normal menstruation and by exogenous metabolism are probably not more than 1 mgm. of iron a day, even diets very low in iron should be sufficient to repair this loss. In the presence of achlorhydria and gastro-intestinal disorder much less iron may be absorbed than normally. Malabsorption of iron and a diet poor in iron may therefore reduce the amount of this element supplied very dangerously near to the amount of iron normally demanded (e.g., about 1 mgm. a day), and if menorrhagia or other pathological blood loss increases the demand (e.g., to 3 or 4 mgm. a day) the conditions for the production of iron deficiency anemia will be fulfilled. It is important to point out, however, that there is no adequate evidence that "idiopathic" hypochromic anemia is an anemia due exclusively to the inadequate supply of iron to the body. Certainly no such conclusions could be drawn from the study of the present series of cases.

Table 7 indicates that sources of iron loss from the body were very common. In only 7 of the 60 cases (cases 54 to 60) did the authors consider that blood loss sufficient to produce the anemia could not be satisfactorily demonstrated. These cases will be discussed individually. In each of them there was the definite possibility that a source of iron loss may have been missed or underestimated.

There were more than 4 pregnancies in each of 28 cases. The total number of pregnancies in these cases varied from 5 to 15. In 16 cases the average time interval between successive pregnancies was only a year and 10 months. It is felt that the short time interval between pregnancies is significant because it does not allow for recovery of the iron lost by the mother, particularly when lactation is prolonged.

Significant pathological blood loss was proved to be present in 53 cases. Menorrhagia occurred in 37 cases, bleeding hemorrhoids in 14 cases, epistaxis in 9 cases, and blood loss from other sources in 8 cases. In the last group there were 3 cases with excessive bleeding following miscarriage, 2 cases with excessive bleeding following parturition, one case of bleeding from duodenal ulcer and later from carcinoma of the sigmoid, 2 cases with gastro-intestinal bleeding from an unknown source.

Combinations of these sources of iron loss from the body were frequently present in any single case. The combination of multiple pregnancies, menorrhagia and bleeding hemorrhoids or epistaxis often occurred. Gray and Wintrobe (73) have stressed the frequency of menorrhagia in this disease syndrome. Before the present study was instituted there were a number of patients coming to the clinic at regular intervals of time in whom no history of pathological blood loss had ever been obtained. In most of these patients after detailed questioning and sometimes by voluntary information on the part of the patient, definite evidence of menorrhagia or bleeding hemorrhoids was obtained. The authors were impressed by the wide variation in what the patients considered normal menstruation. Excessive bleeding at menses in general was minimized because the patient "had always had it," "didn't want to trouble the doctor," "considered that she had a 'good flow,'" was feeling so well since taking iron that she thought it was not important, or because of modesty. It can not be stressed too much that an adequate history of menstrual flow should include the periodicity, the time interval, both the number and size of the napkins used, their saturation, and the amount of flow at night. In obtaining a history of presence or absence of blood in the stools the question must be asked whether or not the patient inspects her stools. Careful questioning is necessary also in regard to epistaxis, which may be an important source of blood loss, and which may be minimized.

Of the 60 cases outlined in table 7 only 7 have escaped discovery of pathological blood loss which could account for the presence of iron deficiency. These 7 patients might be considered to have a purely "idiopathic" iron deficiency, but it is felt that had they been under continuous observation blood loss would have been ascertained. Summaries of the pertinent facts in these cases are given below. They serve to indicate the limits of the criteria which were used to ascertain the presence of blood loss sufficient to produce iron deficiency since even in these cases some blood loss was demonstrated with the exception of case 59.

Case 54. The history of this female patient (Gertrude M.), aged 42 years, was reported in a previous communication (86) concerning her family in which both pernicious anemia and "idiopathic" hypochromic anemia occurred singly and combined. Six years previously she developed symptoms of pernicious anemia and combined system disease. "For years" her finger nails broke easily. She had a tendency to bruise easily. She had been taking raw liver and liver extract for 5 years. Her diet was not grossly abnormal although most of her life she took 8 cups of tea and 6 to 9 slices of bread daily. She had only one pregnancy 20 years previously. Menses occurred monthly, lasted 3 to 4 days and required 4 to 5 pads daily. There was no history of bleeding hemorrhoids or epistaxis. Physical examination gave definite evidence of combined system disease. Gastric analysis revealed no free hydrochloric acid after the injection of histamine subcutaneously. There was a well-marked hypochromic anemia. The hemoglobin rose after iron medication.

(*Note:* This patient was one of the few who were not studied in the hospital ward. Unfortunately no stools were examined for occult blood. It is felt that more complete study might have revealed pathological blood loss. Menorrhagia was present in her 2 older sisters and in one of her nieces.)

Case 55. Female, aged 40 years, single, servant. Her mentality was definitely below the normal. She stated that she was "always anemic" but had noticed pallor and weakness especially in the past 7 years. She had had no pregnancies. Her menses were definitely diminished in amount. Her diet contained meat and a vegetable once daily and was not grossly abnormal. There was no history of blood loss other than the menses. Examination showed prematurely white hair and koilonychia. There was no free hydrochloric acid in the gastric contents after histamine on 2 occasions. Six stools were negative for occult blood except one which showed a positive benzidine test and a negative guaiac test. There was a well-marked hypochromic anemia, with a mean corpuscular volume of 64 cubic micra. The hemoglobin rose to normal after 2 months of iron medication. Iron medication was stopped after 7 months. She was seen at about bi-monthly intervals for 3 years during which time she received no iron medication and the hemoglobin remained between 90 and 95 per cent. During this period of observation she had had occasional small hemoptyses apparently from a small area of bronchiectasis at the left base of the lung. Her menses became about normal in frequency and amount.

(*Note:* No significant source of iron loss was found in this patient.

Anemia did not recur and no iron medication was required during 3 years, and no excessive loss of blood was discovered. It is felt that loss of blood may have occurred in the past and gone unnoticed by an unintelligent patient.)

Case 56. Aged 32 years, married, housewife. Two years previously the patient had had 2 operations on the thyroid gland for hyperthyroidism. For 8 months she had symptoms of anemia with easy fatigue and nervousness. For 2 weeks she was suffering from an abscess at the back of the neck. She had had 2 children and no other pregnancies. Menses were approximately normal in amount and frequency. Her diet was not grossly abnormal, although she had the peculiar habit of chewing about a pound of coffee a week. There was no free hydrochloric acid after histamine both on the initial examination and 5 months later. The abscess of the neck responded to incision and drainage. The hemoglobin rose from a level of 34 to 92 per cent in the course of 3 months of iron medication. When she returned 2 years later the hemoglobin was 62 per cent. She had had a miscarriage of twins with excessive blood loss 5 months previously. The hemoglobin again rose to normal after the administration of iron. When she returned 2 years after this and 4 years after the first observation, the hemoglobin was normal although no iron had been taken for a year and a half.

(*Note:* The later history of this patient seemed to indicate that anemia occurred only when there was iron loss, and it may be assumed that some manner of bleeding may have existed unnoticed before she was first seen.)

Case 57. Aged 65 years, housewife. This patient was first seen in September, 1928, and was observed at periods for a year, after which she never returned to the clinic. Two years previously she was operated upon for appendicitis following which she had a draining sinus for 6 weeks. For a year she had dysphagia, intermittent diarrhea, progressive weakness and pallor. She had had 3 pregnancies. The menopause occurred at 47 years of age. There had been no vaginal bleeding for 18 years. The diet contained meat and vegetables daily. Gastric analysis showed no free hydrochloric acid after the injection of histamine. Gastro-intestinal x-ray was negative. Unfortunately an x-ray of the large bowel was not made. Of 3 stool examinations occult blood was present in one. There was a well marked hypochromic anemia. No rise of the hemoglobin occurred after the administration of liver extract for 3 weeks. After the administration of iron the hemoglobin rose slowly from 43 to 94 per cent in 7 months.

(*Note:* Although no adequate cause was found for the iron deficiency in this patient, it is not unlikely that continued examination of the stools and roentgenological study of the colon by barium enema may have revealed a source of bleeding. Lack of coöperation on the part of the patient prevented complete studies.)

Case 58. Aged 33 years, white, single, female, clerk. Ten years previously she had an obscure illness lasting 4 weeks. Since then she noticed pallor and weakness, and she partook of a meat-restricted diet because of "nephritis." For 2 years fatigue, dyspnea, palpitation and weight loss were noted. She had had no pregnancies. Menses began at the age of 13, occurred monthly, lasted 5 days with normal flow. Her diet contained meat only once a week and very little fruit, and was mostly composed of carbohydrate foods. Gastric analysis revealed no free hydrochloric acid after the injection of histamine. Gastro-intestinal x-rays were negative. Two stool examinations were negative for occult blood. The hemoglobin increased from 31 to 81 per cent in 3 months with iron medication.

(*Note:* Poor diet, achlorhydria and normal menstruation were factors in the production of the hypochromic anemia, but, as has been explained, these do not seem a likely cause of such a profound anemia. The possibility is not eliminated, however, that these factors acting over a period of 10 years may have produced the anemia. At least, any moderate additional loss of blood in this patient may have had a much more pronounced effect upon the hemoglobin level than it would have had in a normal individual.)

Case 59. Aged 57 years, white, widowed housewife. Since the age of 16 years the patient had noticed enlargement of the thyroid gland. Her symptoms seemed mostly related to hyperthyroidism although her hemoglobin was only 45 per cent. She had coughing, choking and palpitation for over 2 years. For 8 months she had been nervous and irritable. She had 2 pregnancies, the last 22 years previously. The menopause occurred 4 years previously. The diet contained very little meat. Gastric analysis revealed the absence of hydrochloric acid after the injection of histamine. The basal metabolic rate was +68 per cent. Examinations of 10 stool specimens were negative for occult blood. The patient's hemoglobin increased from 45 to 70 per cent in the course of 6 weeks of iron medication. Operation for hyperthyroidism was refused. The patient left the hospital and unfortunately could not be reached for further studies.

(*Note:* No blood loss was discovered in this patient. Since she is the only patient of the series with hyperthyroidism, with the possible exception of case 56, it is of speculative interest what the influence of this condition was upon the exogenous iron metabolism.)

Case 60. Aged 40 years, white, Irish housewife. The patient entered the hospital in 1929 because of erysipelas of the face and she was discovered to have anemia. She had had 7 pregnancies in 16 years. Menses began at 13 years of age, occurred about every 30 days with "moderate flow." There was no history of other bleeding. The diet contained only small amounts of meat and vegetables daily, fruit only occasionally, and one or 2 eggs a week. Gastric analysis revealed no free hydrochloric acid after the injection of histamine. Five years later gastric analysis again revealed achlorhydria after histamine. No stool examinations were made. After the administration of iron the hemoglobin increased from 51 per cent to 90 per cent in the course of 3 months. In 1931 the hemoglobin had diminished to 60 per cent, no iron having been taken for over a year. The patient returned to the clinic only at rare intervals. Iron was taken only intermittently. In 1933 the hemoglobin was 70 per cent, in 1934 60 per cent (increasing after 5 weeks of iron therapy to 79 per cent) and in 1936 70 per cent. In 1934 she admitted that her menses had been somewhat increased in amount for 6 months. In 1936 they were definitely increased, as she said, for not over a year. It was felt that she was not very reliable in her statements regarding menstrual flow. She rarely inspected her stools.

(*Note:* Although no definite evidence of abnormal blood loss was obtained, it was felt that a moderate menorrhagia probably was present. Pregnancies probably played a part in the iron deficiency. The patient was not studied completely and was not very coöperative.)

It is assumed that the presence of excessive blood loss in 53 out of 60 cases of "idiopathic" hypochromic anemia is good evidence in favor of the thesis that this condition is a type of hypochromic anemia particularly dependent upon blood loss. Amongst the laity there is great variation of opinion as to what constitutes a normal amount of menstrual flow, and even in the case of persons under medical observation only rough estimations are made. Epistaxis, bleeding hemorrhoids and even moderate gastro-intestinal bleeding are relatively frequent conditions which are often minimized or even unnoticed. These sources of pathological blood loss may be easily missed by even very observing physicians if they are not consciously sought. It is therefore not improbable, in such a series of cases as have been cited, that in certain patients undetermined blood loss may have occurred before the patients came under observation. Presumably, blood loss in these cases need not be as severe as in normal individuals with healthy gastro-intestinal tracts in order to produce a given low hemoglobin level.

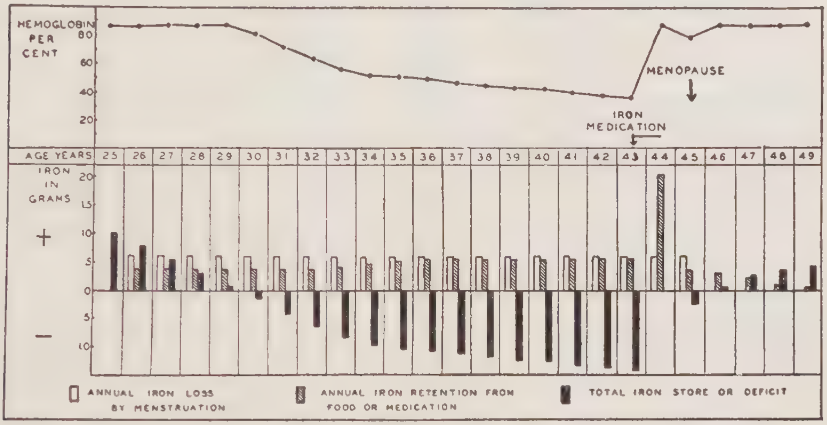

Fig. 4. Hypothetical Case of "Idiopathic" Hypochromic Anemia

This chart shows the conditions which may lead to an iron deficiency anemia in a woman, discovered at the age of 43 years to have a hemoglobin of only 38 per cent. It is assumed that this patient at the age of 25 years had a normal hemoglobin per cent and a normal store of iron in the body (black column). It is assumed that the annual loss of iron by menstruation (white column) was double the normal (600 mgm. per year). It is also assumed that poor diet and perhaps achlorhydria have reduced the annual intake of iron (cross-hatched columns) to somewhat less than the iron loss. These conditions are etiological in many cases of "idiopathic" hypochromic anemia. The iron stores are gradually reduced, an iron deficit sets in, and anemia results. When iron is administered the iron deficit is erased and the hemoglobin returns to normal. When the menopause occurs there is no further need for iron medication and anemia does not recur.

Figure 4 presents hypothetically the conditions which may lead up to an iron deficiency anemia in a woman who has achlorhydria, a diet containing reduced amounts of iron, and moderate menorrhagia. If all the facts concerning the metabolism of iron could be ascertained from day to day throughout years of time in these patients, it is assumed that a balance sheet similar to that given in figure 4 could be set up which would explain the presence of a certain low hemoglobin per cent. In the figure it is illustrated how, after the menopause and

TABLE 8

Hypochromic anemia in adult females in whom after recovery from anemia it was proven necessary to give iron therapy repeatedly or as a maintenance measure because of recurrence of anemia (pathological blood loss was always present)

AGE OF PATIENT	INITIAL R.B.C.	INITIAL HEMO-GLOBIN	ANACIDITY AFTER HISTAMINE (X)	DURATION OF OBSERVATION	SOURCE OF BLOOD LOSS WHICH NECESSITATED REPEATED OR CONTINUED IRON MEDICATION
	million	*per cent*			
47	3.6	45	X	6 months	Menorrhagia
48	3.9	56	X	1 year	Menorrhagia
36	3.6	48	X	1 year	Menorrhagia
28*	2.5	30	0	1 year	Menorrhagia
				2 years	Miscarriage
29	2.7	35		3 years	Menorrhagia
41	4.1	32	X	3½ years	Pregnancy, bleeding hemorrhoids
33	3.7	41	X	2 years	Menorrhagia
38	2.7	33	X	2 years	Menorrhagia
42	1.3	8	X	2 years	Bleeding hemorrhoids
32	4.5	46	X	1½ years	Menorrhagia, epistaxis (following hysterectomy)
41	1.6	14	X	7 years	Menorrhagia
42	3.6	43	X	1 year	Menorrhagia
15*	3.7	50	0	2½ years	Menorrhagia
43*	1.3	11	0	2½ years	Epistaxis (familial telangiectasia)
44	4.5	50	X	4 months	Menorrhagia
35	4.6	48	X	2½ years	Menorrhagia, bleeding hemorrhoids epistaxis
48	3.4	36	X	1½ years	Menorrhagia
45	3.3	31		2 years	Menorrhagia
39	3.7	45	X	2 years	Menorrhagia, epistaxis, miscarriage, with bleeding
36	4.6	57	0	1 year	Menorrhagia
37	3.8	44	X	3 years	Menorrhagia
29	2.7	35		1 year	Menorrhagia
53	3.9	52	0	1 year	Menorrhagia, pregnancy, bleeding, hemorroids
33	3.8	45	X	1½ years	Menorrhagia
35	4.0	52	X	2 years	Menorrhagia, bleeding hemorrhoids (following hysterectomy)
61	3.2	32	X	2 years	Carcinoma of sigmoid
28*	4.6	42	0	4 years	Menorrhagia
44	3.9	54	0	1 year	Menorrhagia
42	4.3	30	0	3½ years	Menorrhagia
42	3.7	35	X	8 months	Menorrhagia
50	2.7	29	X	6 months	Bleeding by bowel of unknown etiology
44	4.6	40	X	1½ years	Menorrhagia
35*	4.0	59	0	1 year	Menorrhagia
39*	3.7	47	0	1 + years	Menorrhagia
40	4.1	51	X	6 + years	Menorrhagia

* Not included among cases of "idiopathic" hypochromic anemia.

TABLE 9

Hypochromic anemia in adult females in whom, after recovery from anemia, it was proven not necessary to continue iron therapy. Pathological blood loss had ceased in all cases

AGE OF PATIENT	INITIAL R.B.C.	INITIAL HEMOGLOBIN	ANACIDITY AFTER HISTAMINE (X)	DURATION OF OBSERVATION NO IRON THERAPY	REASON FOR THE CESSATION OF BLOOD LOSS
	million	*per cent*			
47	3.6	45	X	2+ years	Natural menopause (previous menorrhagia)
32	3.6	34	X	2+ years	No pathological bleeding discovered
36	3.6	48	X	1 year	Hysterectomy (for menorrhagia)
40	3.3	54	0	1¾ years	Spontaneous cessation of menorrhagia
32*	2.3	34	0	3 years	Cessation of bleeding hemorrhoids. (Later recurrence of anemia during pregnancy)
38	2.7	33	X	10 months	Spontaneous cessation of menorrhagia
17*	3.0	37		3 years	Normal menses. (Initial blood loss following abortion)
37	2.9	32	X	1 year	Hysterectomy (for menorrhagia)
32	4.5	46	X	4½ months	Hysterectomy (for menorrhagia) and cessation of epistaxis. (Small doses of iron taken intermittently for 4 years after hysterectomy because of epistaxis, but anemia did not recur)
45*	2.4	30	0	7 months	Cessation of bleeding from duodenal ulcer
49	4.7	50	X	2 years	Natural menopause, cessation of epistaxis
40	3.7	50	0	2 years	Cessation of metrorrhagia and pregnancies
27*	4.4	54	X (Later.)	2½ years	No pathological bleeding (initial anemia associated with postpartum bleeding)
46	3.7	37	X	2 years	Hysterectomy (for menorrhagia)
38*	2.4	28	0	1+ year	Cessation of pregnancies
34*	2.8	62		7 years	Cessation of blood loss from duodenal ulcer (then recurrence of anemia with menorrhagia)
49*	1.8	16		1 year	Hysterectomy (for uterine fibroid and metrorrhagia)
40	4.6	55	X	2½ years	No pathological bleeding discovered
40*	3.5	38	0	4 months	Hysterectomy (for uterine fibroid and metrorrhagia)
67	3.5	34	0	1 year	Spontaneous cessation of bleeding hemorrhoids
35*	4.0	59	0	2 years	Hysterectomy (for menorrhagia)

* Not included among cases of "idiopathic" hypochromic anemia.

after blood loss has ceased, anemia will not recur although iron retention from the food is considerably diminished. A number of cases will be cited in which after cessation of menses anemia did not recur.

One of the reasons given in the past that this disease was "cryptogenic," "idiopathic," or that its probable explanation at least was inadequate iron intake and malabsorption, was that maintenance doses of iron were required in these patients after the hemoglobin had reached normal in order to prevent the anemia from recurring. The disease seemed analogous to Addisonian pernicious anemia in which maintenance doses of liver extract are necessary for the duration of life. This assumption has not been corroborated in the prolonged study of many of the present series of cases. Continuous iron medication, or repeated courses of iron therapy have only been required in those cases in which there was pathological blood loss. No iron therapy has been required after the hemoglobin has reached normal in cases in which pathological bleeding ceased. These cases are summarized in tables 8 and 9. The tables include only females, selected from both the group of "idiopathic" hypochromic anemia and from that of the hypochromic anemia of blood loss. A number of similar cases in men were also seen. In contrast to cases in which initial observations only were made (in 6 of which no pathological bleeding of importance was found) the cases cited in tables 8 and 9 were studied at frequent intervals. It was therefore possible in all instances to correlate the recurrence of anemia with the presence of pathological blood loss, and the maintenance of a normal hemoglobin concentration, when iron was not given, with the absence of pathological blood loss. Recent similar studies of Witts (222) have led to the same conclusion. These observations tend to corroborate the thesis that "idiopathic" hypochromic anemia is a type of the hypochromic anemia of blood loss.

The question will be asked, if a poor iron diet and intestinal malabsorption play only a secondary rôle in the etiology of "idiopathic" hypochromic anemia and if blood loss in some form or frequent pregnancies must be present before this anemia can arise, what separates this anemia from the anemia seen in women due to frank blood loss, or the anemia in women suffering from severe menorrhagia? Why distinguish the anemia by the special term "idiopathic?" It is tempting, indeed, not to use the term "idiopathic" and not to set this anemia apart from any anemia following chronic blood loss. It seems advisable, however, to preserve a special name for this type of iron deficiency because it has seemed a distinct clinical entity to various observers since the original description of Faber, and because blood loss is usually not apparent at first in these patients. The atrophy of the tongue and probably of various parts of the gastro-intestinal tract, together with ectodermal changes, seem to place the condition apart from other types of anemia. The presence of achlorhydria and of the gastro-intestinal abnormalities which achlorhydria presumable signifies, although playing a secondary rôle in the etiology of the disease, is a factor which separates it from hypochromic anemia following blood loss. The absence of acid in the stomach is just as unexplained and "idiopathic" as the achylia gastrica in Addisonian pernicious anemia. Whatever the cause of the anacidity is, there appears to be a constitutional and often a familial hereditary background in women suffering from this form of iron deficiency. As in pernicious anemia, gray or white hair is usually present. The authors have not encountered the true condition in negresses, but Wintrobe and Beebe reported the disease in one negro and two mulattoes (217). Obesity appears to be not as common as in pernicious anemia. Not only is the disease encountered in other female members of the family of a patient, but it is seen also in conjunction with pernicious anemia in a single family, or may even precede or accompany pernicious anemia (58, 221, 86). The constitutional and hereditary factor is therefore important in distinguishing "idiopathic" hypochromic anemia from other forms of hypochromic anemia.

Malabsorption from the intestine should be stressed more than achlorhydria in the etiology of "idiopathic" hypochromic anemia. Hypochlorhydria is sometimes found when the diagnosis seems obvious, although normal acidity of the gastric contents is probably very rarely encountered. In the macrocytic anemias related to pernicious anemia, likewise, normal acidity may be present, for example, in certain cases of sprue. Anacidity, of course, commonly exists in the absence of any anemia (20). The incidence of anacidity gradually increases with age (204, 19) and apparently may be a perfectly benign sympton. In many diseases, for example in sepsis, cancer, nephritis, arthritis, depression of the gastric secretion may take place, to improve with recovery from the disease. It appears that anemia itself often predisposes to anacidity. It is certainly very common to observe anacidity in patients suffering from blood loss and severe anemia, although reduction of acidity is not always the case (3). In these circumstances, normal gastric secretion may be regained when the blood has been repaired. Chang, Yang and Keefer (35) observed improvement of gastric function in certain patients following recovery from "secondary" anemia.

There is good evidence that malabsorption of iron from the food is present in "idiopathic" hypochromic anemia and malabsorption has frequently been considered to play an etiological rôle in this disease. In these patients, the response of the reticulocytes and of hemoglobin regeneration to iron therapy is usually less satisfactory than in patients with hypochromic anemia who have acid in the gastric secretion (147). Nevertheless, other factors than reduction of acid in this disease may interfere with the absorption of iron: there may be anatomical changes of the wall of the small bowel, diminished motility or excess of mucus. Potassium iodide is apparently absorbed more slowly than normal in this condition as well as in other diseases in which a disturbance of intestinal absorption may be present (92). Since acidity favors the formation and preservation of ferrous ions, prevents the formation of insoluble iron compounds, and apparently assists in making food iron available, anacidity has been considered unfavorable to the absorption of iron. Iron given to patients with hypochromic anemia in acid media has been shown to be more effective than iron given in neutral or alkaline media in certain experimental conditions (139). In vitro study has shown that the rate of dialysis of iron and ammonium citrate is increased by acids, decreased slightly by bases (25). In general, disturbances of intestinal absorption have been considered important in the production of various dietary deficiencies (108, 30, 198, 87). Iron, together with certain vitamins and the principle effective in pernicious anemia, apparently is not absorbed by the normal human intestine with ease. Certainly the enormous discrepancy between the effective parenteral dose of iron and the effective oral dose favors this view. It is possible that the absorption of substances of this nature is selectively interfered with when gastro-intestinal disease is present.

Hypochromic anemia associated with achlorhydria and presumable malabsorption of iron occurs in idiopathic steatorrhea (12) and in sprue (33). Just as in "idiopathic" hypochromic anemia, iron loss from bleeding or increased iron demands appear to play the primary part in the etiology.

There is ample evidence that hypochromic anemia responding to iron therapy may follow gastrectomy, and operations upon the stomach. Ivy, Morgan and Farrell (101) called attention to this in dogs. Witts (218) reported a case in a woman who 12 years previously had had a gastroenterostomy performed. Morawitz (150) described different types of anemia including "secondary anemia" following extensive resections of the stomach. Davies (47), Bode and Krumm (22), Lottrup and Roholm (123) and Dameshek (41) reported cases. Meulengracht (142) regarded the functional gastric achylia resulting from gastric operations as probably etiologic in anemia resembling "simple achylic anemia" in all respects, and Hartfall (78) took a similar point of view. Kellogg, Mettier and Purviance (111) showed that the utilization of the iron of the diet was reduced in anemic dogs which had been gastrectomized. Definite proof is lacking in these observations that the achylia gastrica is primarily responsible for the hypochromic anemia. It would appear more probable that as in "idiopathic" hypochromic anemia the achylia is in part, at least, responsible for poor absorption of food iron, preventing recovery from iron deficiency primarily arising from loss of iron or increased iron demands.

Although achlorhydria is present in most cases of "idiopathic" hypochromic anemia, there is evidence that the intrinsic factor of Castle, the interaction of which with beef muscle is curative in pernicious anemia, is nevertheless present (34, 78). Gastric juice obtained from these patients after histamine stimulation when incubated with beef muscle is effective in producing a response of the blood in pernicious anemia. Nevertheless, cases in which both pernicious anemia and "idiopathic" hypochromic anemia are present at the same time have been observed. When beef muscle was incubated with normal gastric juice and fed to cases of "idiopathic" hypochromic anemia by Beebe and Wintrobe (10) no response of the blood occurred. Dameshek (41) observed a moderate reticulocyte response but no permanent hemoglobin response when normal gastric juice was incubated with one-half pound of spinach and 4 egg yolks daily. Mettier, Kellogg and Rhinehart (138), however, were enabled to show a response of reticulocytes and hemoglobin after giving a "predigested meal" of 200 grams spinach, 300 grams beef and 2 eggs, daily.

There remains to be discussed in relation to "idiopathic" hypochromic anemia a phenomenon concerning the stability of the hemoglobin level when the iron deficiency is profound. Although the factors causing a chronic iron deficiency are continuously at work, death from iron deficiency per se rarely, if ever, results. The authors have observed over several years 2 patients who for various reasons were not taking iron medication. The reduced hemoglobin level remained quite constant in these patients. Summaries of the important findings in these 2 patients are as follows:

Case 30. Aged 29 years, American housewife. The patient was first seen in 1931, when she had been having symptoms of anemia for about a year. Her menses were definitely increased in amount. She had occasional nosebleeds. She had had 5 pregnancies in 9 years. Her diet contained very little meat. The red blood cells were 2,700,000 per cubic millimeter. The hemoglobin was 35 per cent. At this time she took iron medication for only a month. However, her diet from this date was quite adequate in protein and vegetables. She did not return until 1932, when the red blood cells were 3,530,000 per cubic millimeter and the hemoglobin 40 per cent. Again, iron was prescribed but was taken only for a month or so. She was not seen again until 1935, 4 years after the first visit, when the red blood cells were 3,260,000 and the hemoglobin 36 per cent. Menstruation had continued to be increased in amount. After she had taken iron medication for only one month the hemoglobin had risen to 84 per cent. Again, she failed to return until 8 months later, in 1936. She had continued iron medication for only 2 months. The red blood cells were 3,660,000 per cubic millimeter and the hemoglobin 46 per cent.

Case 40. Aged 61 years, American widow. This patient was first seen briefly in 1932 and was advised to come into the hospital for study. The red blood cells were 4,600,000 per cubic millimeter and the hemoglobin

40 per cent. She did not return, however, until 2 years later in 1934 when the red blood cells were 3,310,000 per cubic millimeter and the hemoglobin 35 per cent, no iron having been taken in the meantime. The hemoglobin rose to 78 per cent after the administration of iron. There were typical signs and symptoms of "idiopathic" hypochromic anemia. The menopause had occurred at the age of 49. The tongue was atrophic. There were painful cracks at the corners of the mouth. The finger nails were flat and fragile. Gastric analysis revealed absence of free hydrochloric acid after histamine injection. X-ray examination of the gastrointestinal tract showed duodenal ulcer. The stools were positive for occult blood. X-ray studies by barium enema were at first negative but later revealed a carcinoma of the sigmoid from the effects of which the patient subsequently died.

In both these cases the hemoglobin remained at very much reduced levels for long periods of time: in one for 3 years, in the other for 2 years. Blood loss was present in both cases and presumably a poor iron intake as well. Similar cases have been known in which the hemoglobin for many years remained below 40 per cent (145). Several factors may be considered which possibly are at work preventing the hemoglobin from reaching even lower values. It may be assumed that while blood loss is taking place, because the blood is less rich in hemoglobin, less iron is lost from day to day. It is possible that a very low hemoglobin produces an avidity of the gastrointestinal tract for iron and that in these conditions more iron is retained than normally, although this is highly theoretical and presupposes a vital adaptability of the intestine which may not be the case. Reimann (173) speaks of the "rule of the minimal color index," describing the fact that the color index rarely is below 0.5, as though there were a physiologically low limit to the color index which can not be exceeded, true for all types of hypochromic anemia.

The evidence concerning the etiology of "idiopathic" hypochromic anemia may be briefly summarized as follows: there can be no doubt that this disease represents a severe and chronic form of iron deficiency. Associated with this iron deficiency, deficiency of other dietary substances may be present. Blood loss occurring in a chronic and subtle form, as by menorrhagia or bleeding hemorrhoids, can be demonstrated in most cases. Blood loss is believed to be present in practically all cases. Multiple, frequent pregnancies may also be a factor. Diet poor in iron and intestinal malabsorption associated with achlorhydria play a secondary but important rôle in preventing repair of the blood. After iron loss ceases, for example after natural menopause, once the blood has regenerated to a normal level, there is no longer need for iron medication. The etiology of the achlorhydria is unexplained and is "idiopathic" in the sense that it appears to be constitutional or inherited in many cases.

CLINICAL PATHOLOGY

Red blood cells

A hypochromic, microcytic anemia is characteristic of iron deficiency anemia. A red count of 4,000,000 per cubic millimeter and hemoglobin of 40 per cent, giving a color index of about 0.5, can probably occur in no other condition than chronic iron deficiency. In severe cases the color index remains in the neighborhood of 0.5, a condition referred to as the "rule of the minimal color index" (173). Hypochromic anemia, however, is not specific for iron deficiency: a moderate reduction of the color index occurs also in certain other anemias, for example, in severe chronic sepsis and in Cooley's anemia. Color indices of 0.6 to 0.8 are common, especially in the hypochromic anemia following acute blood loss. Indeed, a latent iron deficiency may occur in the presence of macrocytic anemia. This is sometimes seen following acute blood loss and in pernicious anemia and related macrocytic anemias, the typical hypochromic, microcytic character of the red cells appearing after the formation of the red blood cells has surpassed that of the hemoglobin. When hypochromic anemia is advanced, marked anisocytosis and poikilocytosis of the red cells are present, but since the largest cells do not usually exceed those of normal blood, these changes are not nearly so striking as in pernicious anemia. The mean diameter of the red cells is small (172) as are the mean corpuscular volume, mean corpuscular hemoglobin concentration and mean corpuscular hemoglobin (217, 85). Iron deficiency anemia may be present, however, when the mean corpuscular hemoglobin concentration is normal and the mean corpuscular volume and hemoglobin are reduced. The number of orthochromic red blood cells may be less than 10 per cent of the total number (172). The

Price-Jones curves in severe cases show a marked shift of the mode diameter to the left with a fairly broad base (172).

A slight increase of polychromatophilic cells, or reticulocytes, when supravitally stained, is often present in iron deficiency. The reticulocytes vary, as a rule, between 1 and 3 per cent. The number of reticulocytes will be increased if there has been a recent stimulus for their production, as following acute blood loss, and tend to be normal or less than normal in chronic cases. Punctate basophilia and nucleated red blood cells are occasionally seen in severe iron deficiency. In the presence of active blood loss these elements may be increased.

Consecutive daily study of the blood following acute blood loss reveals many changes in the character of the red blood cells. At first, when regeneration of the red cells is active and blood-building material plentiful, there is a response of the reticulocytes. They may reach a peak of 50 per cent of the total red cells but usually are not over 12 per cent. Macrocytosis, in part dependent on the large size of reticulocytes, may be present at this stage, sometimes with a diminished mean corpuscular hemoglobin concentration (90). Gradually, the reticulocytes diminish to normal numbers. In cases in which blood-building material becomes exhausted, hemoglobin formation becomes reduced so that the hemoglobin percentage is static, the production of red blood cells may continue, and the characteristic picture of hypochromic, microcytic anemia develops. It is difficult to say, in such a course of events, at what particular point iron deficiency takes place. In order to demonstrate a reticulocyte response to iron medication it is usually necessary to institute an adequate control period during which the hemoglobin level has remained nearly stationary and the number of reticulocytes has approached normal.

White blood cells

There is no characteristic white blood cell picture in cases with iron deficiency. The total number of white cells is usually normal (6000 to 10,000 per cubic millimeter), but in chronic cases may be reduced to as low as 2500 per cubic millimeter. Such a leukopenia, which is seen commonly in "idiopathic" hypochromic anemia, occurs usually at the expense of all white blood cell elements equally, although sometimes there is a relative lymphocytosis. Multi-nuclear polymorphonuclear neutrophils are occasionally to be found in severe chronic cases. A leukocytosis with predominance of polymorphonuclear cells is common immediately following acute blood loss. The white blood cell picture may vary, of course, with the underlying pathologicl process which may be directly or indirectly producing blood loss and iron deficiency.

Blood platelets

What is true for the white blood cell count is also relatively true for the number of platelets in iron deficiency. In pronounced chronic cases the blood platelets are reduced and increase after the administration of iron as the blood improves. In iron deficiency following acute and subacute blood loss, and commonly in mild cases, however, the platelets are normal or increased in number. The clotting and bleeding times are not significantly altered.

Gastric analysis

Hypochlorhydria and achlorhydria after the injection of histamine are common in chronic iron deficiency as has been discussed in foregoing sections. Achlorhydria after histamine is usually permanent, particularly in cases of "idiopathic" hypochromic anemia. In young male adults suffering from bleeding duodenal ulcer and iron deficiency, the acidity may be normal or even increased (3).

Accompanying the achlorhydria in severe chronic cases of iron deficiency, there is usually an achylia gastrica as well. The total volume of the gastric secretion is much reduced. Pepsin is much reduced or absent. Mucus may be present and Davies (48) has contrasted the presence of mucus in the gastric contents of these cases with its usually relatively small amount in pernicious anemia. It is the impression of the authors that although the gastric juice may be thick and tenacious with mucus, the total production of mucus is usually reduced.

Although hydrochloric acid and pepsin are reduced or absent in most cases of chronic iron deficiency, the intrinsic factor of Castle is apparently present although probably in reduced amounts (34, 78, 31). Gastric secretion obtained from cases of "idiopathic" hypochromic anemia after the injection of histamine when incubated with beef muscle is capable of alleviating pernicious anemia. This demonstrates, of course, a physiological difference between the two anemias.

Other clinical pathological findings

The serum bilirubin in severe, chronic cases is as a rule normal or diminished. The icteric index is usually between 1 and 4. Schmehle and Schmid (181) demonstrated in cases of "simple achylic anemia" reduction of serum pigments and increase after iron medication. This characteristic may be due to a compensatory diminution of the normal processes of cell destruction, or it may reflect a poverty of precursors in hemoglobin formation. The urobilinogen of the urine is usually diminished in chronic iron deficiency.

A point of minor diagnostic importance in differentiating chronic iron deficiency from pernicious anemia is the fact that the urine in the former condition is characteristically light straw in color, in the latter dark yellow or amber, depending upon the difference in excretion of bile pigment derivatives.

A reduction of the plasma protein and of the albumin fraction is common in iron deficiency, as in other types of aemia (94), and may be a factor in the production of edema in certain cases. The plasma cholesterol and lecithin phosphorus tend to be reduced, and to increase when the hemoglobin increases after iron administration (152). The changes are not characteristic for iron deficiency, however. In acute blood loss the plasma lipoids may be normal or high.

The blood iron is reduced approximately proportional to the reduction of the hemoglobin (71). Estimation of the blood iron is an accurate method of determining the amount of hemoglobin. The serum and plasma iron is apparently reduced in chronic cases of iron deficiency, and rises with the administration of iron (178, 127, 149).

PATHOLOGY

Scanty information is available concerning the pathology of the tissues in iron deficiency. This is partly because uncomplicated cases of iron deficiency rarely succumb to the disease, and partly because attention is directed chiefly to the complicating conditions which have produced death. Absence of stainable iron in the tissues should be demonstrable in the liver, spleen, skin and bone marrow, in striking contrast to the findings in hemochromatosis. In animals rendered anemic by repeated bleeding, poverty of iron in these organs has been frequently demonstrated. Autopsy of treated cases dying of complicating disease shows no pathological changes referable particularly to iron deficiency.

The bone marrow has been studied frequently in life, especially by sternal biopsy. It has shown consistently a hyperplastic state with predominance of the more mature nucleated red blood cells (209, 221, 40, 14). This is in contrast to the proliferation of much more primitive red blood cells in the bone marrow of untreated pernicious anemia. The increase of normoblasts in the bone marrow in iron deficiency may be interpreted as a retardation of maturation in the presence of an increased attempt of the bone marrow to supply much needed oxygen carriers (184). The normoblastic proliferation diminished after iron therapy (209).

Suzman (200) reported the autopsy of a case of "Plummer-Vinson syndrome" following death due to traumatic rupture of the esophagus and subsequent infection. During life the red blood cells were 3,500,000 per cubic millimeter and the hemoglobin 30 per cent. There was a history of passing bright red blood by rectum intermittently for 6 years. At post mortem there were no gross pathological changes of significance in the liver, spleen, kidneys, gastrointestinal tract, thyroid gland and other organs. The tongue was as a whole atrophic and the mucous membrane was smooth and glistening. There was a constriction of the superior esophageal orifice and it was felt that a mucosal band had been present before instrumentation, which may have been responsible for dysphagia during life. Microscopic examination of the spleen showed numerous, large immature, unrecognized cells in the pulp with occasional mitotic figures. The bone marrow showed a marked diffuse hyperplasia with both erythropoiesis and granulopoiesis well represented. There were numerous normoblasts scattered throughout. The epithelium of the tongue and esophagus showed a thinning, in some places marked, and a hyperkeratinization. Lymphocytic infiltration was present in the submucosa. The striated and smooth muscle showed degenerative changes and infiltration with fat. No abnormalities were observed in Auerbach's plexus. Microscopic examination of other organs showed no distinctive changes. Microscopic examination of the stomach and intestine was not reported. No report was made concerning visible iron in the tissues.

Schmehle and Schmid (181) reported the autopsy of a case in a woman aged 50 years, who received iron for 3 weeks and then died following operation for myoma of the uterus. Achylia after histamine had been demonstrated during life. There was widespread atrophy of the mucous membranes of the tongue, esophagus and stomach. There were hemorrhages in the mucous membrane of the stomach. The mucous membrane of the whole bowel was pale, spotty red and Peyer's patches in particular were atrophic. In 9 other cases atrophic changes of the stomach were demonstrated by Roentgen ray examination.

DIAGNOSIS

For practical purposes, the presence of hypochromic anemia with the history of blood loss, growth, or pregnancy, often in the presence of a diminished supply of iron, is sufficient proof of the diagnosis to warrant the administration of iron. A specific response of the reticulocytes and of the hemoglobin to iron is corroborative evidence. It should be emphasized that the presence of hypochromic anemia alone is not sufficient evidence for the diagnosis of iron deficiency. The formation of hemoglobin is a complicated chemical process and depends upon the presence of many factors and conditions besides adequate iron stores for completion (88). Thus, iron utilization within the body may be incomplete because of certain inhibiting states or deficiencies of necessary substances other than iron. The administration of iron in these circumstances will not be effective, and it would be misleading to consider such conditions necessarily due to iron deficiency. Hypochromic, microcytic anemia is found in a number of conditions without evidence for iron deficiency. It is seen commonly in chronic infections such as chronic osteomyelitis, in chronic nephritis, and in lead poisoning. In Cooley's anemia, there may be a very marked microcytic anemia. The presence of increased numbers of normoblasts and the very marked poikilocytosis seen in the blood help in differentiating this anemia from iron deficiency anemia. Iron deficiency anemia is easily differentiated from macrocytic anemias, such as pernicious anemia, by the careful determination of the color index, of the size and hemoglobin content of the red cells, or by study of the blood smear. Iron deficiency may accompany other anemias as a complicating factor and should always be suspected when the color index is low.

Since all anemias are accompanied by a reduction of the total iron content of the blood just as they are accompanied by a reduction of the hemoglobin content, the differentiation of iron deficiency anemia from other types of anemia may at times by very difficult. Further investigation of the iron partitives of stroma and plasma may reveal specific differences between iron deficiency and other anemias.

The "secondary anemia" which may accompany chronic disease frequently has a component of iron deficiency: that is, iron medication will frequently alleviate the anemia to some extent. Almost invariably, however, when this is true, factors making for iron deficiency such as growth and blood loss are demonstrable. Chronic sepsis in a growing youth, ulcerative colitis and typhoid fever with bleeding from the bowel are examples of this.

The primary importance of diagnosing iron deficiency anemia often is not in demonstrating a condition amenable to treatment, but in revealing underlying pathology, such as a bleeding lesion of the gastro-intestinal tract. Therefore, a correct conception of the causes of iron-responding anemia may be a valuable aid to the diagnostician. For example, it has been the authors' frequent experience that in adult males after the age of 40 years, hypochromic anemia in the absence of obvious cause signifies occult blood in the stools often from carcinoma of the stomach or colon. Thorough, routine examination of the gastro-intestinal tract in adult patients displaying hypochromic anemia is a worthwhile procedure and will often reveal an organic abnormality.

TREATMENT AND PREVENTION

Treatment

In the treatment of iron deficiency anemia the patient as a whole must be considered. It is not sufficient merely to administer a suitable preparation of iron, but the attempt should be made to dis-cover and to remove any of the possible causes for the iron deficiency and to eradicate if possible any factors tending to inhibit the utilization of iron.

Many articles have been written concerning the treatment of anemia with iron (140, 184, 221, 84, 93). Inorganic iron in the form of many different preparations, rather than organic iron, is the substance of choice. Organic preparations are apparently largely ineffective because the iron present in them is relatively unavailable for absorption. Reduced iron, iron and ammonium citrate, ferrous sulphate, ferrous carbonate in the form of Blaud's pills, and ferrous chloride have been most commonly employed in this country. A clinician may become wedded to a single preparation which he uses in varying dosage. Naegeli (156) stated that since he became acquainted with the value of large doses of reduced iron in chlorosis he has used no other form.

The optimal dosage of iron is much larger than has been usually recommended in the recent past. Table 10 gives the approximate optimal daily dosage of a few preparations, with the approximate iron content. It is to be noted that the iron content of daily optimal amounts of Blaud's pills (U. S. P.) is very similar to that of ferrous sulphate. Ferrous sulphate prepared in pill form, each pill containing 3 to 4 grains of ferrous sulphate, incorporated with a reducing agent such as lactose is much simpler and cheaper to administer than Blaud's pills. The table includes the parenteral dosage of iron and ammonium citrate for comparison. Parenteral administration of iron is not to be recommended except under very unusual and rare circumstances (93). It is painful, toxic and dangerous in large doses. In cases in which absorption of oral iron is very seriously interfered with, as from diarrhea or from extensive surgical operations, or in cases in which medication by mouth is refused by the patient or is contra-indictated, intramuscularly administered iron may be employed. The authors have not as yet observed a single case in which iron given by injection succeeded in promoting blood formation, when by mouth it had failed to do so.

There is a wide variation between the minimal effective dose and the optimal dose for any given case, and the optimal daily dose will vary considerably from patient to patient (84). That large doses of iron often succeed when small doses fail is a fact which has been well proven (140, 184). A small dose of iron given to a case of "idiopathic" hypochromic anemia with achlorhydria may be almost without influence upon the formation of hemoglobin, whereas given to a case of anemia resulting from chronic loss of blood from duodenal ulcer with normal acidity of the gastric contents it may produce a very satisfactory regeneration of the hemoglobin. The dosage as given in table 10 must at times be doubled or even tripled. This is true apparently only in certain chronic cases of iron deficiency and is a rather mysterious phenomenon. Only a small amount of the iron given in large daily oral dosage is utilized in the formation of circulating hemoglobin (in the case of iron and ammonium citrate only about 3.5 per cent (84)). It is possible, however, during the period of rapid gain in hemoglobin, when iron dosage is low, to have as much as 50 per cent utilization. This observation does not mean, of course, that small doses of iron are more effective than large ones.

TABLE 10

Approximate daily dosage of common iron preparations in the treatment of iron deficiency

SUBSTANCE	COMMON METHOD OF ADMINISTRATION	DAILY DOSAGE		
		Grains	Grams	Grams of metallic iron
Ferrous sulphate	One 3 grain (0.2 gram) tablet after meals and before retiring	12	0.8	0.300
Ferric ammonium citrate	One level teaspoon of crystals in ½ glass of milk three times daily after meals with tube	90	6.0	1.000
Ferrous carbonate	Blaud's pills (U. S. P.) four pills three times daily after meals	12	0.8	0.380
Ferrum reductum	Pills or capsules (comprising 15 grains or 1 gram) three times daily after meals	45	3.0	3.000
Ferric ammonium citrate	One cc. of 10 per cent solution intramuscularly twice daily*	3	0.2	0.034

* Iron administered parenterally in this dosage is painful and somewhat toxic, and is rarely if ever necessary. It is included for comparison with oral dosage.

The principles employed in the treatment of the hypochromic anemia of infancy and childhood are the same as in the adult forms of iron deficiency. The optimal dosage of iron has not been studied as thoroughly as in adults but apparently is larger relative to the bodyweight than in adults. It is often necessary to give the iron in liquid form, and a number of satisfactory preparations of easily soluble inorganic iron are available, including iron and ammonium citrate, ferrous chloride, and ferrous sulphate.

There is evidence to the effect that iron is absorbed in the ferrous form, and that iron preparations are effective by virtue of their ability to liberate ferrous ions (187, 188, 174, 121). Ferrous salts, such as ferrous sulphate and ferrous chloride, have been shown to be very effective in small dosage (69, 222). The authors in a small series of cases have determined that 0.8 gram daily of ferrous sulphate (0.3 gram iron) in suitable tablet form is approximately equivalent in potency to 6 grams of iron and ammonium citrate (1.0 gram iron). Ferrous salts tend to oxidize so that preparations should be employed which contain a suitable reducing agent. The administration of 0.8 gram of ferrous sulphate daily, in the form of 3 or 4 suitable tablets given at different times of day, is easily tolerated and very cheap, as Fullerton (69) has pointed out.

In the treatment of iron deficiency anemia attention to the diet is important. Emphasis may be placed on foods rich in blood-forming constituents but the diet for every case is an individual problem. It should be nicely adjusted with respect to all the constituents at an optimum as is proper for any person. Diet is actually more important in the prevention of anemia than its immediate treatment. A history of poor diet and evidence for malabsorption is present frequently in cases of chronic iron deficiency. Associated deficiencies of vitamins and minerals have been observed. Low plasma proteins and edema are not rare. During the time of hemoglobin formation there is a demand for nitrogen which is exemplified by marked reduction of the urinary nitrogen, sometimes by reduction of the total circulating plasma nitrogen (39, 94). About 75 per cent of the nitrogen of normal blood is located in the hemoglobin, a fact not commonly considered. In bleeding ulcer cases, particularly if blood is lost by vomiting, a strict Sippy régime is not advisable. Meulengracht has achieved excellent results in these cases by giving a complete diet (143). Transfusion of blood is rarely necessary in iron deficiency, per se, but of course may be indicated in acute blood loss to restore blood volume and in certain conditions in which iron deficiency is complicated, for example by sepsis.

Although it is advisable, for the reasons which have been stated, to include a diet adequate in proteins, vitamins and minerals in the treatment of hypochromic anemia, there is no necessity for giving routinely additional substances, such as copper, certain liver extracts, bile pigment, chlorophyll and chlorophyll derivatives. This subject has been considered in the section on *Factors other than Iron Influencing Hemoglobin Formation.* Certain of these substances when given with *small doses* of iron have been shown to produce an additive effect upon hemoglobin formation, but their practical value when given with the larger recommended doses of iron has never been satisfactorily demonstrated. Josephs (104) has stated that the combination of copper and iron in the treatment of hypochromic anemia in infants may be more effective than iron alone. There is not complete agreement about this, and in hypochromic anemia in adults the evidence seems to point away from any definite efficacy of copper employed in conjunction with iron (14, 84). Preparations of iron which are employed in the treatment of iron deficiency anemia are contaminated with minute amounts of other minerals. Highly purified preparations of iron, however, are apparently as effective as cruder compounds (14, 84). It is unnecessary to give hydrochloric acid with iron, although in certain experimental conditions which must be well controlled, small doses of iron in the presence of acid have been shown to be more effective than iron without acid or in an alkaline medium (139). In the practical treatment of the anemia of iron deficiency the administration of adequate doses of inorganic iron together with a diet plentiful in protein, vitamins, and mineral-rich foods will satisfy nutritional requirements as they are understood at the present time.

Special pharmacological considerations

The fate of the iron administered orally which is not utilized to form new hemoglobin is at present unsettled. There is no question that most of it is lost in the stool. The metabolism experiments of

Brock and Hunter (24, 23) corroborating those of Fowler and Barer (67), show a wide discrepancy in most cases between the amount of iron apparently absorbed, which may be astonishingly large, and that utilized to form new circulating hemoglobin. Retention of over 6 grams of iron in an experimental period has apparently been demonstrated: more than twice the amount of iron in the entire blood. Further work is necessary to corroborate this and to clarify its meaning. That the body in certain cases can retain large amounts of iron is demonstrated in hemochromatosis in which over 50 grams of iron may be deposited in the tissues. Whether or not this iron can be utilized is unknown. A frequent observation, in cases of "idiopathic" hypochromic anemia which are bleeding, is the prompt recurrence of anemia when iron medication has been stopped. If large amounts of iron had been stored, it would be reasonable to expect that such iron would be utilized to prevent the recurrence of anemia in spite of blood loss. Groen and Taylor (75) have shown in in vivo studies of absorption of iron in the human and the dog intestine, that iron is apparently adsorbed on the mucous membrane and may be recovered by frequent washings. This phenomenon apparently renders it difficult to draw conclusions from in vivo studies upon iron absorption. These are some of the observations which cast doubt upon the conclusions of Brock and Hunter. Their work does not appear to disprove the fact that iron injected parenterally is utilized quantitatively to form new hemoglobin (93, 212).

The response of the blood to iron medication is characteristic and specific. In uncomplicated cases the hemoglobin increases at the rate of one per cent or more per day. The hemoglobin may increase 2 per cent per day, and increases of 3 per cent per day have been seen. There is a slowing of the hemoglobin regeneration as the normal level is approached; when the hemoglobin is over 65 per cent, a rate of 0.5 per cent per day appears to be optimal. The rate of the hemoglobin response and the degree of the reticulocyte response to iron medication tend to be less marked in cases with achlorhydria than in those with acid in the gastric contents (84, 147). Complicating factors such as sepsis, nephritis, cirrhosis of the liver and possibly cancer inhibit the response of the hemoglobin and reticulocytes. The red blood cells increase at a slower rate than the hemoglobin but may reach figures of 6,000,000 per cubic millimeter or more temporarily. This is not to be taken as evidence necessarily that iron acts as a "stimulant" to the bone marrow. There is very little evidence that iron acts in that manner. The evidence, however, that the administration of iron in iron deficiency is a substitution therapy can not be denied. The reticulocytes usually begin to increase within about 3 days after iron therapy is begun and reach a "peak" in from 5 to 10 days, then gradually diminish. There is an inverse relationship between the height of the reticulocyte "peak" and the hemoglobin level. When the level of the hemoglobin is 20 per cent, the reticulocytes usually reach a "peak" of 8 to 16 per cent; when 40 per cent, 4 to 12 per cent; when 60 per cent, 2 to 6 per cent (147).

There is no evidence of tolerance (Gewöhnung) to iron developing after its long continued use. Iron medication may be accompanied by certain disagreeable symptoms and is certainly toxic at times if employed too abruptly in large doses. Patients with iron deficiency seem to tolerate it better than well persons. Malaise, intestinal cramps and diarrhea are common symptoms, particularly when large amounts of iron and ammonium citrate are used. Constipation is not commonly seen when large doses of iron are given. In the author's experience iron medication has no definite influence upon the amount of menstrual flow. Careful analysis of many cases showed an equal number in which menstrual flow increased or decreased following the administration of iron.

Prevention

The prevention of iron deficiency anemia is a significant and important subject; it is linked with the prevention of chronic disease in general, and will be referred to only briefly. Prevention consists, first, in the improvement of hygienic conditions, particularly in the public hospital class of people: dietary education, provision of increased facilities for out-of-door exercise, especially for the young and growing, prenatal care, and elaboration of all the public health activities directed towards the elimination of infectious and chronic disease. Secondly, prevention consists in the early recognition and the removal if possible of the many causes of blood loss.

The prophylactic administration of iron is becoming fairly common.

The prophylactic treatment of the infant begins with the treatment of the pregnant mother whether anemia is present or not (195). Small doses of iron as a preventive are appropriate in infancy and early childhood as well as in girls about the time of puberty (128, 89). The administration of iron in cases of chronic infection and "secondary anemia," in which iron deficiency is not definitely established, is a worthwhile prophylactic measure since it ensures the presence of adequate iron stores for future use when regeneration of the blood takes place.

SUMMARY AND CONCLUSIONS

A deficiency of iron in the body is common and leads to hypochromic anemia. The anemia is, as a rule, quickly alleviated by giving proper doses of inorganic salts of iron by mouth. Iron so given does not act as a so-called "stimulant," but supplies a deficiency, for iron is ineffective in other types of anemia not associated with iron deficiency. How the deficiency of iron comes about is not clear in every case, but certain general rules can be formulated. The body is very sparing of iron. There is no definite evidence that a negative iron balance, that is a loss of iron from the body, can be produced by limiting the amount of iron in the diet. Although 12 to 15 mgm. per day is usually considered to be an optimal iron intake, diets containing much less iron will maintain the iron balance. This is true even though only a fraction of the iron in the food is available to the body. The amount of iron excreted in the urine is practically negligible. Therefore, there is a marked difference between the metabolism of iron and the metabolism, for example, of such elements as nitrogen or calcium, for a loss of nitrogen or calcium may be produced very easily by restricting these substances in the diet. One must search for a loss or an increased consumption of iron to explain in large part an iron deficiency.

There are a number of mechanisms active during different periods of life by which iron may be lost or exhausted. In growth there is a demand for iron to supply in particular the increasing mass of hemoglobin in the expanding blood volume and also to supply the needs for iron of the tissues of the body. In pregnancy there is a demand for iron by the fetus and after parturition for lactation. In women there is a continual demand for iron due to the blood loss accompanying menstruation. These factors of iron consumption and loss must play a primary rôle in the causation of hypochromic anemia, whereas dietary deficiency of iron or malabsorption of iron in a diseased gastro-intestinal tract are of secondary importance. This state of affairs is theoretically true in all dietary deficiency states. First in importance is the loss or increased consumption of the deficient substance and, secondly, inadequate intake.

The recognized types of iron deficiency anemia, some of which in the past have been regarded as of very obscure etiology, are as follows: hypochromic or nutritional anemia of infancy and childhood, chlorosis, "idiopathic" hypochromic anemia, hypochromic anemia of blood loss, and hypochromic anemia of pregnancy.

Iron deficiency occurs in childhood probably because of the excessive demand of growth, inadequate iron endowment from the mother, diets poor in iron and gastro-intestinal disturbances that interfere with absorption. It occurs in girls after puberty usually because of the combined demands for iron of growth and menstruation, together with diets poor in iron. The theoretical demand for iron in a year's time in a girl after puberty is approximately the same as the demand for iron of a normal pregnancy. Chlorosis, although much less common than in the preceding century, has not disappeared and, at least in mild form, is undoubtedly very common. The demand for iron when there is blood loss is obvious. In "idiopathic" hypochromic anemia, which usually occurs in middle-aged women, careful clinical study of cases has shown the very great prevalence of abnormal blood loss, usually from menorrhagia or bleeding hemorrhoids occurring in a subtle and chronic form. Many such cases have had multiple and frequent pregnancies, diets poor in iron, and gastro-intestinal disturbances associated with achlorhydria. The hypochromic anemia of pregnancy results from the demands of the fetus for iron, poor iron reserves, a diet poor in iron and malabsorption of iron. The effect of factors altering the internal metabolism of iron such as infection on the production of anemia requires study and is but one of many aspects of hemoglobin metabolism that remain to be solved.

It seems desirable and reasonable to group all of the various types of hypochromic anemia responding to iron under the term iron deficiency. There is no question that these forms of anemia represent a deficiency disease. Moreover, this is a deficiency disease in which the extent of the deficiency can be determined quantitatively at any time by the determination of the hemoglobin in the blood and in which the deficient factor, iron, can be supplied quantitatively.

In the practical treatment of the anemia of iron deficiency the administration of adequate doses of inorganic iron together with a diet plentiful in protein, vitamins, and mineral-rich foods will satisfy nutritional requirements as they are understood today.

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PNEUMOTHORAX TREATMENT OF PULMONARY TUBERCULOSIS

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I. THE COURSE OF PULMONARY TUBERCULOSIS: THE RATIONALE OF COLLAPSE THERAPY

For many years it was the accepted teaching that pulmonary tuberculosis in the adult arose in the apex and spread to the base. The high incidence of apical scars found at autopsy, which careful studies showed to contain viable tubercle bacilli, and the predilection for the disease to localize in the upper lobes supported this view. At the turn of the present century, however, an increasing number of observers began to take note of the infrequency with which patients with active pulmonary tuberculosis presented themselves with disease limited to the apex of the lung. Sanatoria, established for the treatment of early pulmonary tuberculosis, were being occupied by patients in advanced stages of the disease. It was noted, too, that while 90 per cent of the patients with apical tuberculosis were discharged improved or cured and remained in good health, a majority of the patients with subapical disease died within a few years after leaving the sanatorium. Since the small group of patients with apical tuberculosis constituted the majority of the "cures," the campaign against tuberculosis stressed the importance of early diagnosis when the disease was still confined to the apex of the lung.

At this time, the diagnosis of pulmonary tuberculosis concerned itself chiefly with the finer points of percussion and auscultation of the supraclavicular triangles at the base of the neck. With the increasing use of roentgenology in diagnosis, it was not long before it became apparent that the physical signs, when elicited, were apt to disclose a disease process in an advanced stage. Indeed, the physical examination might reveal nothing abnormal in lungs that were extensively involved. The art of percussion and auscultation gave way to direct roentgen visualization to such a degree that in time no physical signs were considered indicative of tuberculosis unless sputum and roentgen examinations confirmed the clinical findings. The roentgenogram gradually superseded the physical examination for the recognition of the earliest stages of the disease and this, in turn, brought about a modification in the views held regarding the onset of the disease.

Roentgen studies of many patients with pulmonary tuberculosis led to an observation by Braeuning (35), in 1924, that apical tuberculosis seldom evolved into progressive disease. Others soon confirmed his findings. Examination of hundreds of individuals with apical tuberculosis revealed that in only 5 to 10 per cent of such patients the disease showed progressive tendencies. Coincidentally with Braeuning's observations, Wessler (282) in America, Assmann (17) in Germany and later Fishberg (86) and others reported instances of pulmonary tuberculosis that began subapically and developed in a characteristic fashion. The site of origin is in reality subscapular since the lesion arises in the vicinity of the posterior ramus of the superior bronchus, the region that had been described by the French as the "zone d'alarme" years before the advent of roentgen diagnosis. In France, attention had been drawn as early as 1912 by Bezançon and Braun (31) and later by Rist (214) to the sudden pneumonic onset of pulmonary tuberculosis and its lobar localization, a form closely akin to the subapical localization. The belief soon gained prominence, with a few dissenting, that pulmonary tuberculosis in the adult does not arise insidiously from an apical focus but more often suddenly with a tendency towards localization in subapical regions or even in an entire lobe. The latter is often referred to as the "new teaching." It seems, however, that too much emphasis has been placed on the topographic localization of the tuberculous infiltrate and its relation to the apex and too little on the character of the disease itself.

Without going into detail, it can be stated that a clear apex on the roentgen film does not exclude a tuberculous lesion. Adhesions extending from the apex to the chest wall, indicating the existence of apical tuberculous scars, are occasionally visualized on films of patients with presumably subapical tuberculosis who are receiving pneumothorax treatment. Considering the frequency of apical lesions it seems reasonable to assume that apical tuberculosis is often not registered on the roentgen film. Although to be sure, the condition of the apex does not materially detract from the importance of subapical infiltrations in the evolution of progressive tuberculosis, the facts do not seem to warrant the complete substitution of the "old teaching" from the "new teaching." In practice, it does not matter greatly how many centimeters below the apex tuberculosis begins. It may begin at the base of the lung and spread upward. Of greater importance is the recognition of the earliest clinical manifestations of the disease and the necessity for treatment.

Once the disease is well established, its further progress can be studied by serial roentgenograms. Chronic pulmonary tuberculosis does not pursue an even course. The sphere of activity vacillates from one lung to the other and from one portion of a lobe to another, receding in one place and advancing in the second. This occurs simultaneously or sequentially with variable intervals during which the disease appears clinically at a standstill. Following such a lull, the disease lights up, often abruptly, and spreads to other sites. This interplay of progression and recession is best observed in patients under observation for long periods of time. When the disease is slowly recessive, it may appear that healing is universal. When the disease is rapidly progressive, it may appear that destructive processes govern the entire picture. It seems very likely, however, just as the two elements, fibrosis and caseation, in variable degrees, coexist in every tuberculous focus, that there may likewise be a predominance of reparative processes in one organ or part of an organ and, at the same time, destructive processes in other locations. Since the evolution of the disease depends primarily upon the state of immunity of the body as a whole and to a lesser degree on the immunity of the organ involved, these finer immunologic vacillations easily escape clinical recognition.

The course of pulmonary tuberculosis is in essence a clinical corollary of the Koch phenomenon (142). It expresses the tendency on the part of the body that has been infected to eliminate the contents of secondary implantations. Caseation of diseased areas in the lung and ulceration into bronchi results in cavity formation. Expulsion of the cavity contents into other bronchi and blood extension provide means for the dissemination of the disease to other parts of the lung so that all stages of tuberculosis from the miliary tubercle to the giant cavity can be demonstrated in the same specimen. When the tuberculous process evolves slowly and the disease has a tendency to resorb, fibrose, and retract, secondary changes result in the lungs and bronchi, physical alterations occur in the thoracic cage and displacements occur in the thoracic contents which provide a compensatory means for the loss of lung substance. The treatment of pulmonary tuberculosis by collapse measures is largely a matter of supplementing this natural tendency towards fibrosis and contraction by allowing the mechanism greater freedom of action.

The local treatment of pulmonary tuberculosis presupposes a high incidence of isolated lung disease in those age periods where collapse therapy is most frequently employed. This was found to be the case in an analysis of the findings in more than 800 postmortem examinations performed on patients with pulmonary tuberculosis who died of the disease at the Montefiore Hospital in the past twenty years. In approximately 20 per cent of the patients between the ages of 20 and 40 years, the lungs alone were involved. In young individuals, death was usually the result of an acutely progressive tuberculous bronchopneumonia. In older individuals, death was often due to nontuberculous causes. Canalicular spread is one of the characteristic pathways of extension of pulmonary tuberculosis and it is very likely that tuberculosis of the larynx and intestines results in most instances by direct contact with tubercle bacilli swallowed in the sputum. This would explain their unusually high incidence as compared to the incidence of tuberculosis of other organs. Tuberculosis of the lungs, larynx and intestines, very often the three in combination, comprised all the tuberculous changes demonstrable grossly at autopsy in approximately 75 per cent of the patients examined. This does not include the so-called "terminal" miliary tubercles, microscopic in size, that are found in almost every instance if careful search is made of the visceral organs. Of course, the fact that at autopsy one finds many instances of isolated organ tuberculosis does not prove that this represents conditions during life or that disease was amenable to treatment. It merely indicates that tuberculosis in the adult tends to limit itself to relatively few organs.

Collapse therapy becomes a feasible method of treatment of pulmonary tuberculosis if it can be shown that the incidence of its most frequent complications is greatly reduced or, if the latter exist, are favorably influenced by treating the lungs. The following observations seem to bear out this relationship. In the absence of pulmonary cavitation, laryngeal and intestinal tuberculosis are rare occurrences. The rarity of these complications in the presence of apical scars is well known. With advancing pulmonary tuberculosis, laryngeal and intestinal tuberculosis become increasingly more frequent and they are most often present in association with cavitary tuberculosis. For several years we have been accustomed to refer to laryngopulmonary-intestinal tuberculosis as a single disease complex (225, 226). One seldom sees these complications in patients with pulmonary tuberculosis whose cavities are well collapsed by pneumothorax in spite of the fact that tuberculosis of the larynx and intestines is most often encountered in the age groups treated by pneumothorax.

It can also be shown that the character of the disease in the lungs influences the character of the disease in the larynx and intestines. In patients with predominantly fibrotic pulmonary tuberculosis, tuberculous ulcerations in the larynx and intestines occur less often and, when they do occur, are more apt to be limited in extent and show greater tendencies towards healing than is the case in patients with predominantly caseous pulmonary tuberculosis. In patients with laryngo-pulmonary tuberculosis there is often seen improvement in the laryngeal lesion when the pulmonary disease reacts favorably to rest or collapse treatment. At first, a contraindication, the presence of laryngeal tuberculosis is now considered an indication for early collapse treatment. The same probably applies to mild forms of intestinal tuberculosis. The close relationship that exists between a major tuberculous process and a secondary localization is also exemplified by the frequent improvement of tuberculosis of the urinary bladder following removal of a tuberculous kidney.

To recapitulate: Tuberculosis may make its appearance in any part of the lung, the site of election being in the subscapular region of the upper lobe. In the adult, pulmonary tuberculosis is usually limited to the lungs, favorite pathways of extension being to the larynx and intestines. Eradication of active tuberculous foci in the lungs diminishes the incidence of secondary implantations. When the latter are already in existence, improvement of the condition in the lungs favors healing of any tuberculous deposits that may be present in the larynx, intestines and probably in other organs.

Pulmonary tuberculosis of any appreciable duration almost inevitably leads to cavitation. The roentgen film has made physicians conscious of a condition that had been a matter of common knowledge to pathologists for many years. It took some time before physicians were willing to accept the fact that the "annular shadows" which they saw on the film and which were unaccompanied by physical signs were in the great majority of instances pulmonary cavities. It took them a while longer to realize that cavities may develop very rapidly, at the very inception of the disease, and disappear equally rapidly without noteworthy clinical symptoms, the entire process being detectable only on serial roentgen films. At the present time, the diagnosis of cavitation in pulmonary tuberculosis is no longer a matter that requires extended discussion. It is rather the qualitative differentiation of the various types of cavities, their prognostic significance, and the mechanical problems that enter into their formation and obliteration that are now occupying the attention of students of tuberculosis.

It bears repetition that radiography offers the best and frequently the only means at one's disposal in the detection of cavities in pulmonary tuberculosis. Cavities are often inaudible to stethoscopic examination but they are seldom invisible on a well-taken film. Indeed, one occasionally elicits physical signs of cavity that is not verifiable roentgenologically. This is apt to occur when a trachea is displaced and occupies a position adjacent to a fibrotic area in an upper lobe. Many treatises on diseases of the chest still devote a great deal of space to physical signs such as Gerhardt's sign, Wintrich's sign, Friedreich's sign, cracked-pot resonance, and others which have either been disproved or have outlived their usefulness. The space devoted to a description of these signs could be used for radiographic purposes to better advantage. Our concept of what constitutes the physical signs of cavity needs revision. Classical physical findings are occasionally elicited in the presence of large smooth-walled cavities with patent bronchi but not in the presence of recent bronchopneumonic infiltrations with "early" cavitation. Cavities in the middle and lower lobes are particularly difficult of detection on physical examination. In the writer's experience, suppressed or harsh breath sounds and persistent râles, when elicited over a localized area over the upper part of the chest, are indicative of cavitation in practically all patients with pulmonary tuberculosis in whom tubercle bacilli are present in the sputum. The presence of cavitation is all the more likely if the disease has been present for any appreciable length of time and if the patient gives a history of hemoptysis.

Many attempts have been made to classify tuberculous cavities in an effort to ascertain distinguishing characteristics that would enable one to judge their relative prognostic significance. Some investigators (18) have utilized for this purpose Ranke's three-stage classification. Isolated, "punched-out" cavities have been ascribed to hematogenous origin in contrast to thick-walled, fibroid cavities which are believed to be of bronchogenous origin. Although, occasionally, in the presence of a suggestive history and stigmata of hematogenous implantations in other organs, one can hazard such a differentiation, in most instances a clear distinction cannot be made, particularly if the sputum contains tubercle bacilli. A more practical classification has been suggested by Jaquerod (134). This author distinguishes variations in types of cavities depending on the age of the cavity rather than on its developmental characteristics. A somewhat analogous plan has been offered by Pinner (205, 206) who classifies tuberculous cavities according to their form and to the structural peculiarities which they show on the roentgen film. Since his classification deals with mechanical principles, it has been found of value by a number of physicians in the utilization of collapse measures.

Pinner distinguishes three types of cavities: (*a*) "moth-eaten areas in infiltrated parenchyma," (*b*) "round or oval cavities" and (*c*) "fibrotic, irregular cavities." The first two types are pathogenetically young and are amenable to pneumothorax treatment or a phrenic nerve operation. The third type is pathogenetically old and is not amenable to these procedures. His classification is based essentially on the factor of fibrosis and pleuritis which increases with the age of the cavity. This classification is clinically useful providing one takes into consideration the history of the patient and roentgen appearance of the tuberculous process as a whole. We have seen at autopsy "moth-eaten" cavities in patients with predominantly fibrotic pulmonary tuberculosis where there was every reason to believe that the cavities were fairly old. We have likewise encountered a number of instances of thick-walled, fibrotic cavities which the surrounding emphysematous lung tissue caused to appear on the film as round, thin-walled, rarefactions. Too much reliance cannot be placed on the roentgen film alone in distinguishing histological structure.

In general, it can be stated that patients with long-standing pulmonary tuberculosis are apt to harbor thick-walled cavities in the upper lobes which, from the nature of the disease process and the presence of pleural adhesions, are not amenable to pneumothorax treatment except in occasional instances. On the other hand, initial localizations of the disease undergo cavitation of the so-called "early" variety. Because of the frequent subapical location of the latter, pneumothorax is often effective in bringing about their obliteration providing other factors, to which reference will be made later, are favorable. From the recrudescent nature of the disease it is not at all surprising, indeed it is often the case, that by the time collapse treatment is contemplated, one finds old and recent cavities, as well as intermediary forms in the same lobe or in the same lung. Their structure, according to Gloyne (105), is as varied as their number. The symptoms of toxemia are usually due to the recent areas of involvement in the middle and lower parts of the lung. In such instances, pneumothorax is tried first primarily with the aim of bringing about an improvement in the clinical condition of the patient. At times, an effective collapse of the older process in the upper lobe is also accomplished. In many instances, however, the diseased area in the apical region of the lung is adherent to the chest wall and requires supplementary measures to bring about its collapse.

The prognostic significance of the tuberculous cavity has been the subject of many symposia, since the need of collapse therapy is directly related to the problem. Gräff (108), in 1921, expressed his belief that a tuberculous cavity almost invariably portends a gloomy prognosis for the patient. This view has been accepted by others. Recently, Fales and Beaudet (82, 83), Mayer (173) and others have commented upon the large number of instances of cavities that heal spontaneously. Obviously, the two groups are referring to different types of cavities and to different types of disease. The belief of Gräff and his school is based on what the necropsy reveals and rarely is an individual with pulmonary tuberculosis examined at necropsy in whom cavities are not found in the lungs. The more optimistic physicians refer to sanatorium types of patients in relatively early stages of the disease in whom the spontaneous healing of small-sized, recently formed cavities is a fairly frequent occurrence. It stands to reason that the prognostic significance of cavitation in pulmonary tuberculosis cannot be determined from studies of selected groups of patients.

In order to estimate the prognostic significance of cavitation in pulmonary tuberculosis, one should take into consideration the character of the disease as a whole and the symptoms of the patient. McMahon and Kerper (175), Clarke (56), and several others have analyzed a number of factors that influence the healing of tuberculous cavities. Although their statistical deductions serve to confirm well-known clinical observations, it is the lack of proper analysis of material such as was undertaken by these investigators that accounts for the lack of unanimity among different observers. Were careful studies made, it would soon become apparent that the experience of physicians with tuberculous cavities is very much the same. Subapical and centrally located, thin-walled, cavities of 2 or 3 cm. in diameter with little surrounding infiltration and associated with few clinical manifestations, heal spontaneously in a large percentage of patients. Large, thick-walled cavities, particularly those situated in the apex of the lung where they are often surrounded by dense infiltration and pleural reaction, in exceptional instances heal spontaneously.

Noteworthy about the healing of a tuberculous cavity is the fact that although its complete disappearance may require many months, in most instances signs of healing are apparent roentgenologically within a few weeks after the patient is placed at bed rest. A cavity that does not respond early to rest treatment is not apt to be benefited by longer trials. In their important contributions, Fales and Beaudet bring out the fact that small cavities, particularly those associated with exudative disease, heal spontaneously in a large percentage of patients and, what is equally significant, in 95 per cent of instances this occurs within one year. Even in instances of large, productive cavities, the time required for healing is not as long as is commonly believed. In 50 to 66 per cent of their material, healing took place within one year. The bearing of these statements on the indications for pneumothorax treatment and the length of time it should be applied is quite obvious.

The difficulty of determining with any degree of accuracy the incidence of spontaneous healing of tuberculous cavities is understandable. That it occurs with comparative infrequency among unselected groups of patients is strikingly brought out by the individual case reports describing such an outcome athough, it should be added, many observers at the present time consider it superfluous to record such observations. The knowledge that under certain conditions a tuberculous cavity can heal spontaneously does not, of course, lessen the importance of collapse therapy. On the contrary, it provides the foundation for the treatment. Furthermore, this group cannot be used as a control in estimating the value of collapse therapy for the reason that collapse measures are more apt to be used in patients with progressive disease. It does emphasize, however, the desirability of giving a patient a period of bed rest whenever the clinical condition does not call for immediate active treatment.

The treatment of pulmonary tuberculosis by collapse measures depends, in the final analysis, on the experience of physicians who deal with large numbers of tuberculous individuals and who have had an opportunity to study the entire course of the disease. The realization that between 90 to 95 per cent of patients with far advanced pulmonary tuberculosis and 70 to 75 per cent with moderately advanced disease are dead five years after discharge from active treatment (157), is a cogent reason for the utilization of such recognized methods of collapse therapy as have been found to be associated with less risk to the patient than the disease itself. At the same time, it must be remembered that one is dealing with a chronic, recrudescent disease and a method of treatment that has certain limitations and even hazards. The mere fact that statistics prove that the chances of recovery are better with collapse therapy than without it is not an indication for the use of such treatment in any particular instance. The patient in whom an operative interference proves unsuccessful may have been better off had the disease been allowed to run its natural course. Collapse treatment calls for a high degree of individualization of the needs of each patient.

II. THE PROCESSES OF HEALING OF PULMONARY TUBERCULOSIS: THE MODE OF ACTION OF PNEUMOTHORAX

Until the discovery of the Roentgen Ray, our knowledge of the processes of healing of pulmonary tuberculosis depended primarily on what the pathologist found at the autopsy table. As a result, it was believed for many years that fibrosis, calcification and shrinkage were the sole means by which nature brought about arrest of the disease and, in some instances, complete healing. The roentgenogram, by enabling the physician to perform a "living autopsy," while the processes of healing are in a dynamic state, has revealed types of healing that had hitherto not been demonstrable but which many careful observers had suspected of taking place. It naturally followed, with the increasing use of roentgen visualization, that problems should have arisen in the interpretation of lung pathology as depicted on the film which, in the absence of adequate autoptic control, occasioned no little misunderstanding. The deficiency is particularly noticeable when one studies the processes of healing of pulmonary tuberculosis under the effects of collapse therapy. In spite of its many shortcomings, however, the roentgenogram is of the greatest value since the postmortem examination can only reveal the causes of failure of such treatment. It is the rare instance where an individual, having recovered from his tuberculosis, dies of another cause, that one has an opportunity to study the anatomic changes that enter into the processes of healing of pulmonary tuberculosis. Even then it is only the end result of the healing process that can be studied.

Pathology of pulmonary collapse

There are a number of excellent studies on the anatomic changes produced in lungs that had been treated by collapse measures. The reports of Lindblom (154), Gardner (98), Walsh (280), Rolland (221) and Guyon (114) describe 85 such instances and there are many additional reports that describe isolated instances. In very few of the above was it possible to observe the effects of collapse therapy in a lung that responded to the treatment by complete healing, the individual having died of a nontuberculous or nonpulmonary cause. Rolland's patient (case 21) was treated by pneumothorax, which was later complicated by an effusion, for a period of 17 months. Death was due to intestinal and peritoneal tuberculosis. The necropsy revealed dense fibrosis in the left upper lobe which had been originally the seat of an active, bronchopneumonic tuberculosis. A similar instance, reported by Gilbert (101), concerned a young woman who received pneumothorax on the left side for a cavitary lesion in the upper lobe. The treatment was maintained for four years. Death resulted from a contralateral spread of the disease which was also treated by pneumothorax. The necropsy revealed a few fibrotic tubercles in the left lung, well encapsulated, and containing anthracotic pigment but no signs of cavitation.

In the past 20 years, (1914–1933), 54 patients who received pneumothorax treatment for their pulmonary tuberculosis have been examined postmortem at the Montefiore Hospital. The treatment of this group ranged in duration from three to twenty-seven months. Those who received treatment for shorter periods are not included. A study of the material reveals two instances analogous to those reported by Rolland and by Gilbert. In all other respects, the necropsy findings agree with the more detailed observations of Lindblom, Gardner, and the others mentioned. It will therefore suffice to give only a brief summary of the findings.

The 54 instances comprised 42 who had unilateral collapse by pneumothorax, one being supplemented by a phrenicectomy, and 7 who had bilateral collapse by pneumothorax, either simultaneously or consecutively, one also supplemented by a phrenicectomy. In addition to variable lengths of pneumothorax treatment, 5 had thoracoplastic operations, two of these with preliminary phrenicectomy. Although the pneumothorax treatment ranged in duration from three to twenty-seven months, in many instances the lung sustained additional compression during the course of treatment or after its discontinuation by complicating serous or purulent effusions. In 14 of the 54 instances, death occurred from one to six and a half years after the treatment had been discontinued.

The appearance of the lung, as has been pointed out by Gardner, represents the terminal stages of various pathological processes, alterations due to compression, alterations due to associated pleuritis, as well as tuberculous and nontuberculous changes that occur in many instances after the treatment had been discontinued. The pleural cavity on the affected side is either obliterated or else contains a pneumothorax with a variable amount of fluid. The pleural membrane is usually thick and dense adhesions bind the two layers together so that the lung is occasionally macerated in its removal. For practical purposes, it is more instructive to examine the pleural cavity during the course of pneumothorax treatment by means of a thoracoscope than to study its appearance at the autopsy table.

Depending upon the state of the pleural cavity, the lung is found collapsed to a variable degree against the spinal column, especially in the presence of a large effusion, or is found filling the hemithorax. In either case, particularly the former, the lung is considerably reduced in size, is solid, meaty and contains little air-containing tissue. On section, in spite of the reduction in size which may reach a third or a quarter of its normal dimensions, the lung almost invariably contains tuberculous cavities. In some instances, the lung is an excavated shell with a fibrotic rim of lung substance, surrounded by a thick pleural membrane. The nonulcerated parts of the lung are occupied by caseous and fibrotic tubercles. Microscopically, the lung usually does not show evidences of recent disease or much, if any, miliary seeding.

A number of observers have noted that the healthy parts of the lung are not influenced by compression. Complete atelectasis may be present without fibrosis. In patients with advanced pulmonary tuberculosis the pleuritis that results from collapse treatment causes a fibrotic reaction in the underlying parenchyma as well. The extent of the initial disease, the duration of the compression, and the condition of the pleura are prime factors in the production of secondary alterations in the healthy parts of the lung. The bronchi leading to the cavities are usually tortuous and dilated and rarely are they narrowed or obliterated.

The pleural cavity on the untreated side also reveals, as a rule, adhesions that are not, however, as extensive as on the treated side. In 9 of our instances, the pleura was entirely free and in a much larger number the pleural layers were only slightly adherent, usually at the apex. The findings are of some interest in view of the frequency with which bilateral pneumothorax is now utilized. The untreated lung is almost invariably emphysematous and considerably larger than its fellow. On section, the upper lobe contains in most instances evidences of greater or lesser degrees of cavitation. In approximately one-third of our material, cavities were not demonstrable in the untreated lung and in one instance the lung was apparently free entirely from tuberculous changes. Miliary seedings are often seen in the untreated lung, particularly in the course of generalized miliary tuberculosis. This is less often the case in the treated lung. We have encountered several instances where the disparity in the extent of miliary seeing between the treated and untreated lungs was quite marked. Lindblom and Rolland have also noted this phenomenon. In a recent communication, Pagel (196) cites an instance of unilateral localization of miliary tuberculosis in a lung, the freedom of the other lung being due to a chronic atelectatic condition caused by an old and recent exudative pleurisy. The untreated lung is often the seat of a recent tuberculous or nontuberculous bronchopneumonia or both. The intrathoracic displacements that follow collapse of the lung will be discussed more fully later.

Because of their unusual interest, two instances of healing of pulmonary tuberculosis following collapse treatment will be cited in detail.

H. B., aged 43, began to cough and expectorate in the summer of 1921. He also complained of weakness and loss of weight. He was admitted to the Montefiore country sanatorium in November, 1921, where physical and roentgen examinations revealed an advanced pulmonary tuberculosis in the left lung with cavity formation. The sputum was positive. During the first year of his stay, he gained 30 pounds in weight and felt well. Subsequently, the disease took a turn for the worse and he was given pneumothorax on the left side. Pneumothorax treatment was maintained for several months, until January, 1923, when he developed a pleural effusion. The effusion later became purulent and contained tubercle bacilli but no secondary organisms. In the course of the next five years, the patient developed a marked sinistrocardia, adherent mediastinitis and a traction diverticulum of the oesophagus. The latter part of his life was characterized by marked dyspnea, cyanosis, frequent hemorrhages and difficulty in swallowing. The roentgen films revealed marked fibrosis in both upper lobes, the later films showing evidences of cavitation in the right lung. He died in June, 1929. The postmortem examination revealed the following:

No fluid was found in either pleural cavities. Both lungs, especially the left, presented moderately dense fibrotic adhesions particularly at the apices. The left (treated) lung was removed with some difficulty. The upper lobe consisted of a dense, anthracotic, greenish, airless mass. The lower lobe was slightly crepitant and congested. Cavitation was not demonstrable. The right lung showed a marked degree of compensatory emphysema. A portion of the upper lobe projected in a tongue-like manner over the mediastinal structures. On its anterior surface there presented a large depressed puckered scar to the under surface of which the main bronchus was adherent. On section, the right lung revealed a large irregular cavity extending out into the tongue-like process. From this cavity, thick bloody fluid material exuded. Section through some of the lumpy areas that could be palpated from the outside showed small irregular areas of caseous yellow material. Elsewhere, in the lung could be seen firm, partly fibrotic and partly anthracotic nodules. Microscopic examination of the lung revealed in some sections almost complete replacement of parenchyma by caseous material showing central hemorrhage. In other sections, the tissues showed numerous, parallel, spindle-shaped cells of fibromatous character. Many of the alveoli were plugged with large foamy cells characteristic of tuberculous bronchopneumonia.

M. E., 19, entered Montefiore Hospital in March, 1914. She became ill about seven months before her admission with cough, expectoration, night sweats and afternoon fever. In the first four months she lost 15 pounds in weight but regained some of the weight later. The physical and roentgen findings of the chest revealed an advanced tuberculosis in the right lung with a large cavity in the upper lobe. The left lung showed infiltration at the hilus region. The sputum was positive. A month after her admission, pneumothorax was induced on the right side and from then on large injections of nitrogen, ranging in amounts from 600 to 1000 cc. at positive pressures, were injected into the right pleural cavity, at irregular intervals. The plate revealed collapse of the right lung and marked displacement of the heart to the left. After six months of treatment, she developed an empyema which did not reveal tubercle bacilli. She died in January, 1915.

The postmortem examination revealed the following: The right chest cavity was completely filled with about two liters of seropurulent fluid. The pleura was $\frac{1}{8}$ to $\frac{1}{4}$ inch in thickness and presented a very rough, irregular surface consisting of purulent exudate and fibrin. At the upper angle of the pleura, a number of fibrous strands crossed the pleural space between the lung and wall. The right (treated) lung was compressed against the spinal column to between one-third to one-fourth of its normal size. It appeared as a densely organized layer of lung tissue covered by a thickened pleura. There was no evidence of cavitation. The left lung was voluminous in size, emphysematous and showed a few moderately firm adhesions at the apex. In the left apex a cavity was present, containing a small amount of pus. The rest of the upper lobe was diffusely infiltrated with miliary tubercles. The lower lobe was congested and edematous.

The first instance illustrates a marked degree of healing in a lung, initially the seat of an advanced tuberculosis. The cavitation that had been present in the left upper lobe was not demonstrable at the necropsy. That the pneumothorax served primarily to initiate a native ability to heal the disease is evidenced by the subsequent autosterilization of the empyema and its complete absorption as well as the healing of several subcutaneous cold abscesses and a bronchopleural fistula. Furthermore, there were present in the larynx and intestines tuberculous lesions which also showed considerable evidences of healing.

The second instance illustrates the therapeutic effect which the hydrostatic action of an effusion sometimes exerts on a tuberculous process. In this patient, too, cavitation was not found in the treated lung although present prior to pneumothorax treatment.

Physiology of pulmonary collapse

The physiological alterations that follow collapse of a lung by pneumothorax have been studied both clinically and experimentally (37, 181, 212). These have been investigated with respect to the changes produced in the air, blood and lymph supply of the lung and the effects of these changes on the healing of the tuberculous process itself. Manifestations of the former are often noted within a short time after the institution of the treatment; the latter become evident much later, in some instances after the treatment is discontinued. Physiological alterations, it must be emphasized, are not confined to the lung that is collapsed. The thoracic cage acts as a unit and the effects of compression of one lung are transmitted to an appreciable degree to the other. What may appear, offhand, as a paradoxical type of treatment, such as contralateral pneumothorax, finds a rationale in this mechanism.

According to Christie (55), the first effect of the injection of air into the pleural cavity is to immobilize the chest wall. As the pneumothorax becomes larger, it causes a decrease in the distensibility of the lung and a decrease in the blood flow so that both from a respiratory and circulatory point of view the lung is very effectively rested. From a therapeutic point of view, Christie emphasizes the importance of the resulting passive hyperemia in the collapsed lung. The contralateral lung is overworked, both the blood flow and ventilation are increased, the deleterious effects of such overwork on any tuberculous lesion in the good lung being possibly offset by the active hyperemia which results. Bronchospirometric studies by Jacobaeus (129) and his associates, by means of which it was possible to collect the air from each lung for separate analyses, have also revealed a reduction in the air exchange on the affected side.

Williams (284) noted that compression of the lung results in tortuosity, strangulation and obliteration of the vessels. The blood vessels of the opposite lung are distended. The circulation in the lung varies with and is dependent on the degree of overdistension or compression, and the functional integrity of the right ventricular myocardium to compensate for the increased resistance in the lung. Hilton (125) and Tørning (266) arrived at similar conclusions. The latter observed that with moderately large pneumothoraces, the pneumothorax-lung's share of oxygen absorption and circulation decreases with the fall in its ventilation, at the same time oxygen absorption and circulation of the contralateral lung increase to such an extent that the total oxygen absorption and minute volume are but little affected. With the pleural pressure above zero, the pneumothorax-lung's ventilation and oxygen absorption are arrested and the minute volume diminished. There is considerable lymph stasis in the collapsed lung.

There have been comparatively few observations made on the effects of collapse measures on the bronchial channels although such studies offer a fertile field for investigation. The interruption of free bronchial communication very likely plays a rôle in the isolation of the disease in the early months of treatment and this may be instrumental in the obliteration of small cavities (158). In several instances we have noted large cavities occupying the major part of an upper lobe show rapid diminution in size following the institution of pneumothorax of limited extent. In these instances, as we had occasion to verify by bronchoscopic and lipiodol studies, it is not unlikely that bronchial obstruction may have been instrumental in the striking change that took place in the size of the cavities. We have seen two instances where sudden bronchial occlusion during pneumothorax treatment gave rise to characteristic symptoms and signs of massive collapse of the lung. Similar observations have been made by others (1, 252).

Coryllos (63), a prominent exponent of the rôle played by bronchial occlusion in the healing of pulmonary tuberculosis, believes that the efficacy of collapse treatment is largely influenced by the interruption of free bronchial communication to the lung. The resulting anoxemia produces an anaerobic environment that is detrimental to the growth of the tubercle bacillus. In addition, he believes, the decreased quantity of oxygen favors the development of fibrosis within the lung substance. It is difficult, however, to conceive of an anoxemic state in a partially collapsed lung that would be significantly bactericidal for the tubercle bacillus. The demonstrability of collateral respiration through alveolar pores (162, 274) and the known viability of the tubercle bacillus in dense scars and calcareous foci speak against anoxemia per se as being of much significance in the healing of the disease.

Although it is difficult to correlate the processes of healing of pulmonary tuberculosis with the element of bronchostenosis, there is no doubt that the early disappearance of tubercle bacilli from the sputum, in many instances within a week or two of treatment, and their occasional reappearance after a lapse of time, suggest that a mechanical factor is at play in the early months of treatment. Of our patients who received pneumothorax and whose sputum became negative and remained persistently so, 45 per cent lost their tubercle bacilli within the first three months and 76 per cent, within the first six months following pneumothorax induction. Véran (275) noted that in 59 per cent of his patients the tubercle bacilli disappeared from the sputum within the first six months and in 88 per cent within the first year of treatment. Bendove and Reiss (22) found the incidence to be 50 and 82 per cent, within three and six months, respectively.

The immediate symptomatic improvement in the patient's condition, the fall in temperature and the early decline in the velocity of erythrocyte sedimentation that frequently follow a successful pneumothorax can be ascribed to the physiological isolation of the lung by mechanical interference with its air, blood and lymph supply. The effects appear too soon and are too striking to be explained in any other way. This is borne out by the fact that where the collapse is incomplete, the symptoms may be temporarily aggravated while the most spectacular results follow complete collapse of the lung. When the pulmonary collapse is of appreciable duration, the effects of the treatment on the tuberculous process itself come to the foreground.

Healing by resolution

At its onset, pulmonary tuberculosis is an acute inflammatory disease similar in many respects to nontuberculous pneumonic infections.

The healing process at this stage differs little between the various types of pulmonary inflammations excepting for the fact that the healing of tuberculosis takes place more slowly. In tuberculosis, much of the inflammatory exudate surrounding the tuberculous bronchopneumonic foci is of a nonspecific character which, however, cannot be differentiated clinically or roentgenologically from the specific tissue inflammation. It is believed by many that healing by resolution is particularly characteristic of tuberculous inflammatory tissue where the nonspecific element plays a major rôle in the exudative reaction. At any rate, under proper conditions, both the perifocal and focal exudates may absorb and serial roentgenograms of such nonulcerated areas reveal a gradual resolution of the process. The end result, as depicted on the roentgenogram, often reveals lung markings that are indistinguishable from the surrounding healthy lung structure. Whether or not a microscopical scar remains within the lung substance is for practical purposes of no importance (79).

When a recent tuberculous process in the lungs undergoes caseation and cavitation, the probability of resolution, as Amberson (4, 5) pointed out, decreases more or less proportionally as the extent of caseation increases. The process of healing in such instances is analogous to that which takes place in nontuberculous suppurative disease. The wall of the cavity in the early stages of tuberculous bronchopneumonia, as noted by Gloyne (105), is composed of lung parenchyma (arterioles, venules and capillaries, respiratory bronchioles and alveoli). The wall is not distinctly formed and contains a minimal amount of connective tissue. With the sloughing out and absorption of the caseous elements the antrum itself becomes in time obliterated. In the opinion of Jaquerod (134), compensatory hypertrophy of the lung surrounding such caseous areas plays an important part in the healing process. Serial roentgenograms reveal a gradual absorption of the exudate surrounding the cavity and a thinning out of the cavity margin. There is concentric contraction of the rarefied area, the boundary zone becomes increasingly less distinct until no signs are left to show that the tissue had once sustained a loss of substance. In some instances, there is noted, coincidentally with the contraction of the rarefied area, a greater condensation of the boundary zone with the appearance of a small amount of fluid in the cavity. Healing by resolution has been duplicated experimentally (99) and there are on record instances where such an occurrence was corroborated by postmortem examination. Most of our knowledge, however, of this type of healing has been derived from serial roentgen observations of patients with labile forms of pulmonary tuberculosis.

The processes of healing of recent forms of pulmonary tuberculosis under the effects of collapse treatment differ in no way from those occurring spontaneously. In the presence of pneumothorax, the collapse measure usually employed in such instances, the tempo of healing is possibly accelerated, where this faculty is present, but not the nature of the process itself. When the healing faculty is lacking, as in experimental animals, collapsing a tuberculous lung does not inhibit the process of caseation (61). As might be expected, in instances of recent forms of pulmonary tuberculosis which have a tendency to heal by resolution a partial collapse of the lung often suffices. Furthermore, results are obtained in a comparatively short time. A number of reports are on record (66, 104, 234) where a partial pneumothorax under low tension given for a few months was followed by complete healing of an early tuberculous process. After the pneumothorax is absorbed, as in instances of spontaneous healing, there may be little demonstrable on the roentgen film to indicate that the lung had been the seat of a tuberculous process or that pneumothorax had been employed in the treatment.

Healing by fibrosis

Although some degree of resolution probably accompanies the healing of most forms of pulmonary tuberculosis, complete healing by resolution is the exception rather than the rule. More often a fibrotic scar of greater or lesser extent remains in the lung to indicate a healed lesion. There is no necessity here to describe the transformation of a caseous focus into a fibrotic scar. Adequate descriptions are available in treatises on the pathology of pulmonary tuberculosis. Fibrotic areas in the subapical region have a tendency to retract upward and to occupy an apical position. The compensatory enlargement of the uninvolved parts of the lung probably aids in this migration. The scar formation occasionally results in traction dilatation of the bronchi, a condition we have described elsewhere (227). Usually the healing process is accompanied by some degree of pleuritis and the resulting anchorage of the lung to the chest wall modifies the forces of healing within the lung itself.

The significance of calcification as a means of healing of pulmonary tuberculosis has been overestimated. As Jaquerod (134) points out, calcification is not a sign of healing but is a byproduct of caseation. Once the disease is well established, the incrustation of caseous foci with calcium salts has probably little effect on the final outcome.

The tuberculous cavity may heal by fibrotic transformation. At times, the entire cavity is converted into a fibrotic scar. In rare instances, particularly in the aged, only the wall of the cavity heals by metaplasia of the lining membrane or, as Fried (95) suggests, by epithelialization of the latter from the adjacent bronchial mucosa. In instances of small sized cavities, there is an increased fibrous proliferation and a gradual contraction of the cavity space until there is apposition and fusion of the walls and, in time, complete conversion of the tissues into a dense fibrotic mass. In instances of large cavities, partly because of the considerable loss of lung substance and rigidity of the wall and partly because of the associated pleuritis and fixation of the lung, complete fibrotic transformation of the cavity is less likely. In these, the end result is often a distorted, slit-like opening, the unobliterated part of the lumen retaining a variable amount of caseous matter. The partially occluded cavity is imbedded in dense, indurated lung tissue which serves to keep the disease in a confined area. Potentially, there is always some risk associated with this type of healing although the patient may remain well for many years.

Under the effects of pneumothorax, the collapse measure that is usually attempted first, the healing processes of advanced, ulcerative pulmonary tuberculosis are of the same nature as those we have just outlined. The collapse of the diseased part of the lung has to be fairly complete and has to be maintained for several years before one feels safe that healing has taken place. In contrast with the type of tuberculosis previously described, where healing takes place mainly by resolution and where the degree and the duration of the collapse are subsidiary in importance to the immunologic state of the individual, in fibroulcerative pulmonary tuberculosis it is the character and the duration of the collapse of the diseased parts of the lung that determine the eventual outcome.

Healing by retraction: fibrothorax

This type of healing of pulmonary tuberculosis is a frequent occurrence in patients with predominantly unilateral, fibroulcerative disease particularly in individuals of middle age. In addition to the marked degree of pulmonary fibrosis and shrinkage there are two other elements, atelectasis and pleuritis, which alone or together play a significant rôle in the causation of a condition, aptly described by Vincenti (276) as fibrothorax. As a result of shrinkage of the affected lung and the enlargement of the contralateral lung, the heart, trachea and mediastinum are displaced to the affected side producing a dextro- or sinistrocardia, the latter being the more frequent. Pleural adhesions aid in this process. The affected side of the chest wall is drawn inwards and the diaphragm upwards and this allows a greater degree of pulmonary contraction. It is interesting to note that a similar condition can be duplicated experimentally (144) by ligating branches of the pulmonary artery or veins leading to the heart and it may well be that an analogous state of affairs, to a lesser degree, is present clinically as evidenced by the circulatory phenomena that so often characterize this condition.

The lung is frequently the seat of an extensive bronchiectasis and emphysema. The emphysema in both lungs may be of such degree as to cause rupture of vesicles into the visceral pleura with the formation of blebs which sometimes reach large proportions. We have encountered a number of instances where such emphysematous blebs ruptured and produced spontaneous pneumothoraces. The evolution and course of such pneumothoraces resemble more the so-called "idiopathic" rather than the tuberculous variety. Although, as a rule, the pleura is involved in the process, there are instances where the same results are noted with the pleura uninvolved, the condition being due to bronchostenosis and atelectasis of the affected lung (123, 195).

The tuberculous process becomes partly organized and partly remains caseous. The shrunken lung becomes encased in a thick membrane and the disease is clinically arrested. The symptoms of which the patient complains are occasionally caused by the cardiac, tracheal, oesophageal and gastric displacements as well as by the associated emphysema and bronchiectasis. We have encountered several instances where patients suffered more as a result of the healing process than they did of their initial disease. Pulmonary retraction associated with intrathoracic displacements is a frequent occurrence following collapse procedures. It occurs very often in individuals who had received pneumothorax that had been complicated by an effusion.

Were the processes of healing as simple as we have outlined, pneumothorax treatment of pulmonary tuberculosis would present comparatively few problems. In practice, however, absorption, fibrosis and retraction, to varying degrees, enter into the healing of nearly every form of chronic pulmonary tuberculosis, if not at one phase then at some other phase of the disease. It thus becomes necessary to choose a type of treatment that answers the needs of the moment and, at the same time, one that will fit into a program for future use in case the initial measure fails of its objective or the disease extends beyond the range of its therapeutic effects. This demands the fullest coöperation between the physician and the thoracic surgeon and a clear understanding of the problems presented by each individual patient.

III. INDUCED PNEUMOTHORAX: HISTORICAL; INDICATIONS; CONTRAINDICATIONS

The initial suggestion that air be allowed to enter the pleural cavity as a means of treating pulmonary tuberculosis is generally credited to James Carson (1822) (52) although, it is claimed, several physicians had commented previously on the possibilities of such a method of treatment. In the case of the latter, however, it is not always clear whether the physicians aimed to induce a collapse of the lung or to incise and inject solutions into the diseased tissues. It was Carson, studying experimentally the physiology of circulation and respiration, who first attempted the treatment in the human being. Furthermore, it is to Carson's credit that he held forth greater promise for the procedure than was warranted by his initial experiences. In spite of his failure to affect favorably the course of the disease in two patients in whom he tried the method, he maintained "a surgical operation held out the only prospect of curing that disease."

In 1835, the idea of puncturing the chest and thereby suspending action of the diseased lung occurred to another Scotchman, an American physician, Daniel McRuer (177). We are indebted to Lawrason

Brown for making this historical discovery and to Waring (281) for its popularization. That McRuer had a keen insight regarding the indications for the procedure may be gathered from his following restrictions: "When the disease is confined to one lung; when pleuritis is not present; when there is still remaining stamina sufficient to enable the system to recover." In this concise statement, he expresses the ideal indication, the most frequent complication and the factor that determines the results from the treatment. There is no record that McRuer ever put his idea into practice.

In the same decade several English physicians, notably Houghton (1832) (127) and Stokes (1837) (258) remarked on the favorable course which tuberculosis occasionally took following spontaneous rupture of the lung. Their observations, as well as those of the physicians mentioned previously, failed to arouse medical interest until almost a half a century later when Toussaint (267) confirmed their observations that collapse of a tuberculous lung sometimes favored healing. It was the latter's thesis, in 1880, in which he described 9 instances, among 24 collected from the literature, of the beneficial effects of spontaneous pneumothorax or hydro-pneumothorax on the course of pulmonary tuberculosis, which Forlanini acknowledged later as having been responsible for the development of his own idea of inducing pneumothorax in the treatment of pulmonary tuberculosis. In 1882, Forlanini published in detail the theoretical considerations that prompted him to advocate pneumothorax for the treatment of pulmonary tuberculosis (92). Lojacono (156) has recently translated Forlanini's original contribution into the English language.

Prior to Forlanini's first clinical report in 1894, dealing with his experiences with pneumothorax in the treatment of pulmonary tuberculosis, a case report entitled "Haemoptysis treated by the induction of pneumothorax so as to collapse the lung" was published by Cayley (53), in 1885. Cayley's presentation referred to a porter, aged 21, who had recurring haemoptyses. He was treated by pneumothorax by means of an intercostal incision on the supposition that "the presence of air would arrest the hemorrhage and if there were active development of tubercle in progress in the lung, this would probably be checked." In the discussion that followed, Parker suggested that pneumothorax be induced by injecting filtered and carbolized air through a needle rather than by means of an intercostal incision. From the remarks of Symonds and Ewart and the editorial comments in the same number of the Lancet, in which Cayley's report appeared, it seems that the treatment of pulmonary tuberculosis by pneumothorax was beginning to engage the attention of English clinicians at about the same time that Forlanini was engaged in his epoch-making studies in Pavia.

As a matter of historical record, it is safe to assume that although the idea of inducing pneumothorax occurred to physicians prior to Forlanini and, in a crude manner, was attempted in several instances, it was Forlanini who established the treatment on a scientific basis. His detailed monograph in 1912 (93) is a scholarly exposition of the indications and the modus operandi of the treatment and contains the germ if not the substance of many "original" discoveries made later by others. It is primarily due to Forlanini's interest in the subject and to his pupils that Italian physicians have continued to occupy a prominent place in phthisiology, particularly in the "Forlanini treatment" of pulmonary tuberculosis.

Three years following Forlanini's contribution, Murphy (1898) (186), of Chicago, apparently unaware of the former's work, presented at the annual meeting of the American Medical Association, at Denver, a paper entitled, "Surgery of the Lung," in which he also advocated the induction of pneumothorax in the treatment of pulmonary tuberculosis. He cited eight instances treated by this method. In the following year Murphy's pupil, Lemke (149), reported in detail the histories of 53 patients treated by pneumothorax. Lemke's death, at the age of 30, and Murphy's unwillingness to engage further in pneumothorax for fear it would interfere with his chosen field, surgery, are believed to be responsible for the delay in the utilization of pneumothorax treatment in America. The adoption of the procedure in Germany is credited to Brauer (1906) (36). Its subsequent popularization in Europe is linked with the names of Dumarest (75), Saugman (238), Lillingston (153) and others. The revival of interest in pneumothorax treatment in America through the contributions of Mary Lapham, Robinson and Floyd, Hamman and Sloan, and others, is detailed in Waring's monograph, "The History of Artificial Pneumothorax in America." Today, pneumothorax is almost universally used in the treatment of pulmonary tuberculosis.

Indications

When Forlanini attempted "to peer into the field of the future therapy of pulmonary phthisis," he did not realize that his idea of inducing pneumothorax would, in time, revolutionize the treatment of the disease. At the present time the value of pneumothorax treatment is no longer a matter that requires extended discussion. Its general indications are fairly well established. The pressing problem is to define the scope of the treatment in order to bring it within the reach of the greatest number of patients. How early in the disease should pneumothorax be applied and how late in the disease is its use still justified? These problems are assuming increasing importance with the increasing incidence of early diagnosis of pulmonary tuberculosis, on the one hand, and with the increasing use of selective and bilateral collapse measures, on the other. Furthermore, an increasing number of instances fall in borderlands where it is a question of choice of one measure or combination of measures in preference to another.

There are many physicians who advocate the institution of pneumothorax in patients with minimal pulmonary tuberculosis (slight infiltration without demonstrable cavitation; tubercle bacilli may or may not be present). It would have taken considerable courage on one's part to have advocated the induction of pneumothorax in such instances fifteen or twenty years ago. Today, proponents of pneumothorax in the treatment of minimal pulmonary tuberculosis are increasing in number. Myers and Levine (187) found that their results in instances of minimal disease were much superior to those obtained in other groups of patients. They cite several authorities who share the same opinion. Cedric Shaw (245) is quite emphatic regarding the value of pneumothorax in patients with minimal tuberculosis. All of his patients, after a short stay in the hospital where pneumothorax was induced, were treated in a clinic. On the basis of comparisons between 184 patients who had sanatorium treatment as well as pneumothorax and 83 who had pneumothorax alone, Shaw concludes that the influence of sanatorium treatment, aside from its educational value, is not of primary importance as an accessory to pneumothorax. Recently, Turner and Collins (271) compared the results of pneumothorax treatment in patients with minimal pulmonary tuberculosis with a group of patients who did not receive the treatment. They found that the total period of disability and the sputum conversion time were definitely decreased in the former group. The physicians of the City of Chicago Municipal Tuberculosis Sanitarium (58, 59) are subscribing enthusiastically to the scheme of early pneumothorax treatment not only for its value to the individual patient but also as a public health measure on the premise that collapsing a tuberculous lung is a better means of diminishing the spread of the disease than isolation of the patient. This phase of the problem will be dealt with more fully later.

The majority of physicians who advocate the immediate institution of pneumothorax in patients with minimal pulmonary tuberculosis restrict the indication to include such instances where the disease is active or is showing signs of progression. Obviously, this is begging the question since it presupposes a variable period of observation of the patient. In substance, physicians who advocate the institution of pneumothorax in patients with minimal, progressive pulmonary tuberculosis consider the character of the disease more important than its extent as a guide to treatment. Few physicians at the present time disagree with this view, except that each one has his own idea as to what typifies minimal pulmonary tuberculosis, what characterizes active disease and what constitutes an adequate period of observation. Since minimal, progressive, pulmonary tuberculosis, in practice, is a rara avis, one is more often dealing with a disease that is moderately advanced and often far advanced.

There is another group of physicians who believe that pulmonary tuberculosis in its initial stages does not require any other treatment aside from rest and hygienic care. But on closer analysis of this "conservative" attitude, one finds that, with isolated exceptions, the physicians of this group share essentially the views of their "radical" colleagues. This group also advocates pneumothorax if the disease, regardless of its extent, is progressive or does not show evidences of retrogression within a reasonable length of time. Proponents of the latter view include such authorities as Amberson (6), Davies (71), Dumarest (76), Fishberg (87), Gravesen (109), Matson (165) and many others. The final decision, in any individual instance, has apparently little to do with one's radicalism or one's conservatism.

It rests primarily with one's interpretation of the character and course of the disease, with the equanimity with which one views the matter of collapsing a tuberculous lung and with the facilities available for a preliminary investigation of the patient's needs.

There is much to be said for the school that advocates a period of watchful waiting before embarking on a program of collapse treatment. It bears repetition that the initial infiltrate, even in the presence of cavitation, heals spontaneously in quite a large number of patients. Every physician of experience can recall instances where he advised pneumothorax and by the time the patient consented to the treatment the disease had undergone spontaneous healing. The initial infiltrate, moreover, is almost invariably confined to a single lobe. Pneumothorax may necessitate the collapse of the entire lung and this may result in permanent functional impairment of the healthy lobes, particularly if an effusion should occur. Lindblom (155) has shown that an exudate causes deterioration of the functional capacity of the lung through fibrotic changes in the pleura and in the sound lung tissue. Shaw had nine serous effusions and two empyemas among his 43 patients with minimal pulmonary tuberculosis treated by pneumothorax. In general, the maintenance of a free pleural space for any length of time is not a desirable thing.

Many physicians advocate immediate pneumothorax in the belief that any delay favors the formation of pleural adhesions, the chief obstacle to a successful collapse of the lung. Careful studies (50), however, have shown that adhesions depend primarily on the location of the cavity and its proximity to the pleura rather than on the duration of the disease. In the treatment of recent tuberculosis in the subapical parts of the lung, a month or two of observation can be utilized with comparative safety insofar as the danger of the formation of adhesions is concerned. Peters (199) made the observation that adhesions are most often encountered in patients with either hyperacute or chronic disease. In the former, the early institution of pneumothorax would be indicated by the nature of the disease; in the latter, time would not be the important element in the problem.

In view of the foregoing considerations, it seems preferable not to institute pneumothorax in patients with recent forms of subapical disease of limited extent without a preliminary period of observation.

The deciding factor is the availability of proper facilities for such an undertaking. In view of the labile character of the disease, frequent roentgen examinations are indispensable. In addition, one has to study the vital signs, the sputum findings and the results of repeated blood sedimentation tests. The ideal plan is to hospitalize the patient immediately in an institution devoted to diagnosis and treatment. Here the patient can be observed for several months, if necessary, and a final decision reached. In some instances, it may be advisable to transfer the patient to a country sanatorium for a prolonged period of rest, or else, if pneumothorax is induced and produces a successful collapse of the lung, the patient may be referred to a pneumothorax clinic or to a physician's office for further treatment. If the patient, for one reason or another, cannot enter immediately a tuberculosis institution, the treatment will depend on the patient's clinical condition. In the presence of symptoms of active disease, pneumothorax should be induced immediately either in the patient's home or in a general hospital. If the patient has slight constitutional symptoms, it may be possible to keep him in bed at home and his condition followed in the physician's office or in a clinic until a decision is reached regarding further treatment.

A few physicians induce pneumothorax in their offices or in clinics. One questions the advisability of doing this even in programs of collapse therapy that aim at mass treatment of as many individuals as possible. Pneumothorax does not take the place of bed rest. The one supplements the other. The writer is fully aware, however, that there is an increasing tendency on the part of many physicians to take matters into their own hands at the earliest possible moment and not to rely on the whims of nature. The increasing use of pneumothorax in the treatment of earlier and earlier stages of pulmonary tuberculosis has led Heaf (120) to remark that "some day somebody will get up and say that we should collapse the lung to prevent the onset of tuberculosis." That we are not far from this state of affairs is evidenced by the fact that infants as young as 14 months have been lately treated by pneumothorax in an effort to combat the effects of the primary infection (141).

There is no doubt that the early application of pneumothorax tends to shorten the period of hospitalization in favorable instances. This truism has been utilized by a number of physicians as an additional reason for early induction, particularly in the treatment of patients of the working class who are public charges. At the same time other physicians maintain that the need of immediate pneumothorax is not so urgent in the treatment of patients who can afford a prolonged period of bed rest. From a medical standpoint, the economic condition of the patient has no relation to the need or to the type of treatment to be employed. Unfortunately, the economic factor does play a major rôle in the results obtained.

Although the presence of cavitation in the lung and tubercle bacilli in the sputum, in view of their prognostic significance, are motivating forces in the treatment of pulmonary tuberculosis, it is a mistake to consider these factors per se as indications for collapse treatment. One does not treat the cavity but the underlying disease. This concept is tenable in spite of the fact that the results from treatment depend primarily on the success with which the collapse causes the obliteration of cavities. In the following discussion, reference will be made to several groups of patients commonly seen in tuberculosis practice in whom pneumothorax is indicated either as a treatment of choice or of necessity or, occasionally, as a palliative measure. No particular emphasis will be placed on the existence of cavities in the lung or tubercle bacilli in the sputum. Their presence is to be taken for granted.

Many patients in whom pneumothorax is employed reveal unilateral, fibroulcerative disease in the upper half or third of the lung with cavities of moderate size in whom the disease had existed for an appreciable length of time. The contralateral lung is either free from disease or, more often, contains an inactive, fibrotic process in the apex. This group meets the classical indications for pneumothorax since in many instances the patient had had a period of comparative rest either at home, or in a health resort usually, however, not under strict medical supervision. In a certain number of instances, particularly when the cavities are of small size, healing may ensue with a prolonged period of best rest. It is the consensus of present-day opinion, however, that this group of patients is best treated by pneumothorax, particularly if the cavities are more than 2 or 3 cm. in diameter. When the disease is associated with considerable expectoration pneumothorax is the treatment of choice. In the presence of fever, rapid blood sedimentation and other evidences of constitutional imbalance, pneumothorax is a matter of necessity and is indicated at the earliest possible moment.

Another group of patients in whom pneumothorax is indicated presents a widespread tuberculosis in the major portion of the affected lung from apex to base. The condition is particularly frequent in the left lung of young women. Multiple, small cavities are usually present. The symptoms are of moderate severity. In many instances the heart is displaced to the affected side and the increased density on the roentgen film suggests the presence of lobular atelectasis or thickened pleura. In several instances we have had an opportunity to examine films after lipiodol instillation and to visualize a stricture in one of the main bronchi, the latter being also verified by bronchoscopic examination. If the disease is of comparatively recent onset, pneumothorax can be induced in most instances with surprising ease. If left untreated, the disease may eventuate in a condition of fibrothorax to which reference has been made elsewhere.

There is a group of patients in whom there is present extensive, fibroulcerative tuberculosis, predominantly unilateral, with large cavities in the upper lobe and smaller cavities and caseous foci in the middle and lower parts of the lung. The disease is almost invariably associated with some degree of pleuritis. Pneumothorax is tried with the hope that the resulting collapse, if necessary with the aid of additional measures such as intrapleural pneumonolysis or phrenicotomy, may cause sufficient fibrosis in the diseased lung to enable later the employment of thoracoplasty. Occasionally pneumothorax alone proves successful even in the presence of large cavities in the upper lobe. In view of the fact that the disease usually shows clinical evidences of activity and the contralateral lung is seldom free from disease, an attempt at pneumothorax induction is indicated as early as possible.

Pneumothorax is used for want of anything better in the treatment of patients with acute, caseous pneumonic and bronchopneumonic tuberculosis. The symptoms closely resemble pneumococcal pneumonia and the disease is often confused with the latter because it is apt to be nonulcerative in the beginning and tubercle bacilli are late in making their appearance. The disease is most often noted as a dense consolidation in the right upper lobe clearly delineated by the interlobar fissure. Less often the disease involves the left upper or one of the lower lobes. We have had occasion to treat a number of patients presenting such lesions on the wards of the Morrisania City Hospital (229). The disease is often seen in the Negro. In the majority of instances, the disease progresses in the same lung or to the contralateral lung in spite of pneumothorax treatment. Occasionally, the treatment is followed by temporary improvement but a cure is seldom obtained. Similar discouraging results have been obtained by others particularly in the treatment of bronchopneumonic tuberculosis.

Hemorrhage has always presented an ideal indication for pneumothorax and the results are often spectacular particularly in the so-called inflammatory or congestive types of hemoptyses. When the hemorrhage is due to rupture of a blood vessel in a rigid cavity that is adherent to the chest wall, collapsing the surrounding healthy lung may be ineffective or may even aggravate the bleeding. The purpose of collapsing a tuberculous lung in the presence of hemorrhage is not to produce hemostasis,—few patients die of hemoptysis,—but to prevent aspiration of tubercle bacilli into the uninvolved parts of the lungs. In patients with unilateral disease hemorrhage is of no greater significance as an indication for pneumothorax than are any of the other symptoms denoting active disease. The presence of hemorrhage makes the indication more urgent. In many instances, patients with advanced disease are treated by pneumothorax initially for hemostatic purposes and the treatment, although otherwise unsuccessful, is maintained indefinitely and no attempt is made to treat the disease itself. Once the bleeding ceases there is no reason for continuing pneumothorax treatment unless it serves a purpose.

Pneumothorax is employed as a measure of "last resort" in patients with advanced disease involving predominantly one lung and also an appreciable extent of the "good" lung. Although, occasionally, a satisfactory result is obtained, this does not occur often enough to warrant the extended use of pneumothorax for such purposes. The risks associated with the treatment should deter one from using pneumothorax as a palliative measure except under unusual circumstances. This brings up the question, "How late in the disease is pneumothorax still justified?" Although it is difficult to draw a sharp line between therapeutic and palliative pneumothorax, on the whole, one is inclined to agree with the conclusions reached by Peters, Pope, Morriss, Packard and Miller (200) in their statement: "As we continue to extend the indications for pneumothorax therapy, as has rapidly been done in recent years, we must expect a much larger proportion of unsatisfactory results, and may, in a certain group of cases, arrive at a point where it is questionable if there are any worth-while results. . . . The disadvantages of an unprofitable and fruitless pneumothorax should always be borne in mind."

There are certain groups of patients for whom a number of physicians prefer to employ other collapse measures in preference to pneumothorax as primary procedures. Nehil and Alexander (190), O'Brien (193), Lambert (146), Morin (184) and others are of the opinion that temporary or permanent paralysis of the diaphragm is superior to pneumothorax in the treatment of recent circumscribed disease. They advocate phrenic nerve interruption not only in basal tuberculosis but also in the treatment of upper lobe and midzonal cavities of moderate size providing they are surrounded by healthy parenchyma and have a tendency toward fibrosis. If the phrenic operation fails, pneumothorax can be tried later. In the presence of fever or other symptoms of active disease, it is generally agreed that there is no substitute for pneumothorax.

In the presence of fibrotic cavities limited to the apex of the lung, Coryllos (64), Davies (71) and several others advocate partial, "selective" thoracoplasty in preference to pneumothorax. It is claimed that the results are unusually good and the operative risk comparatively slight. Moreover, pneumothorax is usually unsuccessful because the apex of the lung is apt to be adherent to the chest wall. Davies holds to the opinion that for a considerable number of patients it is ultimately a saving of time by treatment with initial bed rest and later, if necessary, some form of plastic operation. He considers this preferable to induced pneumothorax with the attendant inconveniences and risks of the latter. But in view of the fact that one cannot foretell the presence or absence of pleural adhesions without an attempt at pneumothorax, the majority of physicians do not subscribe to this plan.

It is a natural tendency on the part of physicians to decry treatment by rote. But until such a time arrives when physicians will be able to prognosticate with greater assurance the course of future events, the treatment of pulmonary tuberculosis will continue along a more-or-less beaten pathway. Although there are occasions when experimentation is justified, in the vast majority of patients pneumothorax is the treatment to be tried first. If pneumothorax proves unsuccessful either alone or in combination with intrapleural pneumonolysis or diaphragmatic paralysis, thoracoplasty comes into consideration. In most instances the path of major thoracic surgery is prepared by preliminary treatment by pneumothorax.

It has been stated on many occasions, and rather glibly, that there is a time in the course of pulmonary tuberculosis when every patient may have the benefit of collapse treatment. As a generalization, this belief serves a wholesome purpose; as a working hypothesis, this view is untenable. In some instances, one has many months in which to decide upon any particular line of treatment; in other instances, the disease is not amenable to collapse treatment from its inception. Although, as a rule, it is preferable to begin with minor measures it is wrong to continue such treatment for any length of time if the treatment fails of its objective. In the past the tendency has been to utilize minor measures long after they had proved unsatisfactory with the hope that the treatment would ultimately be successful. This is no longer good practice. The modern approach to collapse treatment of pulmonary tuberculosis calls for a certain degree of conservative radicalism, an attribute difficult to develop and more difficult to apply.

Pneumothorax is occasionally indicated in the treatment of pleural complications of pulmonary tuberculosis. The tuberculous etiology of dry pleurisy is problematical in view of the difficulty of correctly diagnosing the condition but pleurisy with effusion is generally considered tuberculous unless proven otherwise. This view has been recently corroborated by bacteriological studies of the gastric contents of patients with serous effusions as well as by refined culture methods of the fluid itself. Pneumothorax replacement of primary tuberculous serous effusions has many supporters but most physicians disapprove of the procedure as a routine method of treatment. The latter claim that repeated chest puncture is apt to convert a sterile effusion into an empyema. A serous effusion rarely develops into an empyema unless a pneumothorax is present. Furthermore, the hydrostatic pressure of the fluid is an effective means of healing any existing subpleural tuberculosis that may be present in the lung, if not too extensive. In any event, the fluid tends to reaccumulate and obliterative pleuritis sets in regardless of one's effort to keep the lung collapsed by pneumothorax. In view of the foregoing, the majority of physicians believe that primary tuberculous serous effusions should not be aspirated except for symptomatic reasons. This practice coincides with the findings of the empyema committee of the American Sanatorium Association (203) and with the views recently expressed by Trail (268). Patients who develop serofibrinous effusions secondary to demonstrable active pulmonary tuberculosis present a different problem. The treatment of this group of patients will be discussed elsewhere.

Spontaneous rupture of the lung with resulting pneumothorax, occurring in the course of active pulmonary tuberculosis, is frequently mentioned as a condition that calls for conversion into a therapeutic pneumothorax. It was the occasional "providential" outcome of spontaneous pneumothorax in the tuberculous that led to the adoption of pneumothorax as a therapeutic measure. In practice, however, it is the rare instance of tuberculous pneumothorax that lends itself to conversion. Either the disease is bilateral and advanced or else the pneumothorax is small and encapsulated or, if the pneumothorax is complete, one has an empyema to contend with. In instances of tuberculous pneumothorax there is more often occasion to withdraw air than to instill air. If the disease is unilateral and the pneumothorax is fairly complete, the collapse of the lung should, of course, be continued. At the present time, individuals are treated with pneumothorax relatively early so that the problem of converting a spontaneous pneumothorax into a therapeutic one is not often encountered.

The close association of tuberculosis of the lungs, larynx and intestines has been commented upon in a previous chapter. This applies to therapy as well as to diagnosis and prognosis. The systematic examination of the larynx in all patients with pulmonary tuberculosis has brought out the fact that the larynx may be diseased without any symptoms and that with improvement in the pulmonary disease, there is coincident improvement in the laryngeal disease. This is probably also true with regards to mild forms of tuberculosis of the intestines but one cannot prove the latter as readily. The clinical and radiological findings of intestinal tuberculosis are usually of a disease that is an advanced stage.

The presence of laryngeal tuberculosis is an additional indication for therapeutic pneumothorax in patients who otherwise present a disease suitable for collapse treatment. The resulting improvement in the general condition of the patient, the lessened irritation caused by the diminished cough and expectoration and possibly the decreased opportunities for reinfection with bacilliferous sputum, all favor the healing of the disease in the larynx. No single factor can explain the beneficial results obtained since healing can take place in the larynx in the presence of tubercle bacilli in the sputum. St. Clair Thomson and Trail (265) noted improvement in tuberculosis of the larynx in adults following pneumothorax treatment of the lungs. Dworetzky (77) has collected data from many sources of patients with laryngopulmonary disease whose laryngeal lesion improved or healed following collapse treatment of the pulmonary disease.

Diabetes mellitus is a frequent complication of pulmonary tuberculosis whose presence calls for early institution of pneumothorax treatment. From January 1, 1925 to January 1, 1936, 57 patients with diabetes and pulmonary tuberculosis were treated by pneumothorax at the Montefiore Hospital. During this period approximately 150 patients with both diseases were admitted to the tuberculosis wards. Considering that 29 or 50 per cent of the patients were past the age of 50, it is obvious that one finds particular need of pneumothorax in the treatment of the tuberculous diabetic. This is due to the fact that in the diabetic, pulmonary tuberculosis is apt to be of recent onset and progressive in nature. In 90 per cent of our patients the combination of the two diseases was associated with a bad prognosis (230). The tuberculosis has a tendency to localize in the subapical and basilar regions of the lungs and to undergo cavitation rapidly. Hemorrhage is particularly frequent and is often the cause for the institution of pneumothorax. The results from pneumothorax treatment in this group of patients, more so than in the nondiabetic group, depend on the strict unilaterality of the disease and the effectiveness of the collapse. The latter is obtained with surprising frequency considering the advanced age of the majority of the patients. On the whole, the results from pneumothorax treatment of tuberculous diabetics are not as good as in patients without complicating diabetes. Temporary improvement is obtained in many but durable results in few.

Pneumothorax finds a fertile field in the treatment of pulmonary tuberculosis in adolescents in view of the fact that this age group has not shared in the declining mortality of the disease since the beginning of the present century. A recent report by Armand-Delille (12) refers to an experience with over 600 instances of tuberculosis in adolescents treated by pneumothorax. Because of the tendency for tuberculosis to progress at this age, pneumothorax is the treatment of choice even in instances presenting few symptoms. The recent character of the disease allows the establishment of a satisfactory pneumothorax in most instances. From an experience with 91 patients, between the ages of 12 and 21 years, Brock and Mullen (38) conclude that, if the diagnosis is made early enough and a successful pneumothorax is established, the results from the treatment are quite satisfactory for white patients but to a lesser degree for Negroes. Tállyai-Róth (260), during a period of ten years, utilized various forms of collapse therapy in 567 women aged 16 to 20 years. The majority were treated by pneumothorax and supplementary procedures. The results from pneumothorax were exceptionally good in those in whom it was possible to maintain the treatment for at least three months. Peters (200) and his associates also advocate the wider use of pneumothorax in the group under twenty years of age.

In any large series of cases, one finds that approximately 70 per cent of the patients treated by pneumothorax are between 20 and 40 years of age, the largest single group comprising those between 20 and 25 years of age. A small number are in the fourth decade of life but past the age of 50 few individuals are found suitable for pneumothorax treatment. Closer investigation reveals that the reason one finds few indications for pneumothorax treatment in aged individuals is primarily due to the character of the disease rather than the age of the patient. In a study of 414 individuals with pulmonary tuberculosis past the age of fifty (230), the writer found that recent forms of pulmonary tuberculosis in the aged can be treated by pneumothorax in spite of the frequent coëxistence of arteriosclerosis, hypertension, emphysema and other senile changes. This was exemplified in the treatment of a number of elderly diabetic individuals in whom the pulmonary tuberculosis was of recent onset. Several years ago we had occasion to treat on the wards of the Montefiore Hospital a man 70 years of age who had diabetes and an exudative tuberculosis in the left lung. Following six months pneumothorax treatment, an effusion developed and inflations were discontinued. The disease became arrested and the sputum free from tubercle bacilli. In the past year we had a similar experience in the treatment of a woman, 76 years of age, who had diabetes and a lobar tuberculous consolidation in the right upper lobe. A selective pneumothorax was obtained; the sputum became negative within one month and, except for one occasion, remained negative ten months later, at the time this report was written.

Although the initial clinical evidences of pulmonary tuberculosis are discovered in most instances in the right upper lobe, collapse therapy is more often applied in the treatment of left-sided disease. This discrepancy is more apparent when one analyzes separately the two sexes. Pneumothorax and other collapse measures are applied with approximately the same frequency to the right and left lungs of men but in from 55 to 60 per cent of women these measures are applied to control left-sided pulmonary tuberculosis. This finding is noted repeatedly in reports dealing with large numbers of patients. Apparently, the left lung more so than the right, in women particularly, is apt to harbor progressive tuberculosis that requires collapse treatment. A number of explanations have been advanced for this occurrence (228).

The greater incidence of pulmonary tuberculosis in the Negro as compared to the white race has focussed the attention of many investigators on possible differences in racial susceptibility, on environmental predisposing causes as well as on psychic and autonomic factors that may explain the unusual degree of vulnerability of the Negro to tuberculosis. Physicians who have had an opportunity to study the pathological peculiarities of tuberculosis in the Negro believe that there is a distinct difference in comparative racial resistance. The essential variables in the Negro consist in the greater incidence of exudative forms of tuberculosis and widespread pneumonias with rapid cavity formation and the relative infrequency of chronic forms of pulmonary tuberculosis with their associated tendencies towards fibrosis and healing. On the other hand, physicians who understand the peculiar psychic make-up of the Negro ascribe considerable significance to the fact that although the Negro may be aware of his condition he endeavors to conceal it as long as possible so that he comes under medical supervision late in the disease. Negroes, it is claimed, possess a relative lack of sensitiveness to bodily discomfort and even pain and are in greater fear of being put under restraint than is the case among white individuals (279). The economic condition is, of course, a decisive element in the control of tuberculosis in the Negro and is stressed by all. It appears very likely that a combination of several factors are responsible for the high death rate from tuberculosis among this neglected group of the population.

The indications for pneumothorax treatment of pulmonary tuberculosis in the Negro, as might be expected, depend not only on the character and extent of the disease but to an appreciable degree on the several incidental factors which have been mentioned. Pulmonary tuberculosis in the Negro calls for immediate and intensive treatment. Because of the danger that the patient may not fully cooperate with the physician, it may be necessary to employ what may seem drastic measures in the treatment of relatively early forms of pulmonary tuberculosis. One cannot temporize with any form of treatment that is only partially successful. The need may arise for the employment of irrevocable measures such as phrenicectomy or thoracoplasty in order to insure that the lung remains collapsed after the patient leaves medical supervision. The above, in brief, has been the experience of physicians who have had an opportunity to treat large numbers of Negro patients.

Although many reports are on record describing the influence of pregnancy on the course of pulmonary tuberculosis, and several on the effect of tuberculosis on pregnancy, generalizations based on statistical deductions of past events are of little value in deciding the best type of treatment to be employed in the individual case. On the basis of statistical comparisons, many physicians claim that pregnancy does not exert any deleterious effect on tuberculosis while others are equally emphatic in their belief that pregnancy constitutes a distinct hazard. To a considerable degree the difference of opinion is due to a lack of proper definition of terms relating not only to the disease but also to the pregnancy. But inasmuch as constants or yardsticks of any type are apt to meet the requirements solely of their originators and in view of the fact that economic and social considerations as well as the future welfare of the child are of major importance, the problem of pregnancy and tuberculosis will always remain a highly complex one. It may be taken for granted, however, since few physicians fail to have misgivings when pulmonary tuberculosis and pregnancy are associated and most physicians advise their patients not to become pregnant unless their disease is well healed, that the combination of tuberculosis and pregnancy will continue to present special problems in treatment. The reader is referred to a comprehensive review of the subject in a recent monograph by Jameson (133).

The treatment of a parous woman who has pulmonary tuberculosis depends on the stage of the pregnancy and the character of the disease. Gravesen (109) advises abortion in the early months of pregnancy and, if the disease is suited for collapse treatment, the institution of pneumothorax. If the pregnancy is too advanced, he advocates pneumothorax under low tension and the induction of labor six weeks before the completion of term. After delivery, the pneumothorax can be pushed to complete the collapse of the lung. Rist (215), who firmly believes that the association of tuberculosis and pregnancy leads to an extension or a reactivation of existing disease, except in those with mild and fibrotic types of tuberculosis, recommends pneumothorax in all suitable cases as soon as possible. In a recent report, Rist and Jottras (216) tabulate the results from pneumothorax in 132 pregnant women. Exceptionally good results (63 to 67 per cent "cures") were obtained in 58 patients in whom pneumothorax was instituted prior to the pregnancy. In 74 women in whom pneumothorax was induced during pregnancy, the results depended on the stage of the gestation. During the first four months the successful results amounted to 53 per cent; during the last five months, 38 per cent. It is the consensus of opinion that the best results are obtained if pneumothorax is instituted early in the pregnancy and is maintained throughout the period of gestation as well as during the puerperium and for several years thereafter. There are a number of instances on record of bilateral, simultaneous pneumothorax successfully carried out in pregnant women (96, 217).

Pneumothorax has been used with varying degrees of success in the treatment of a variety of nontuberculous pleural and pulmonary diseases. In spite of the fact that encouraging results are occasionally obtained, collapse measures have not met with general acceptance in the treatment of nontuberculous diseases of the lungs. The reason is not difficult to find. The raison d'être of collapse therapy in the treatment of any pulmonary disease is that the treatment be of aid to natural processes of healing. If the treatment does not meet this prerequisite, there is no indication for collapsing a diseased lung. On the contrary, the procedure is more apt to be associated with danger. If, for example, drainage from a mesially located lung abscess can be facilitated by means of a small pneumothorax, such treatment is justified. If, on the other hand, the abscess is not draining or is situated subpleurally, pneumothorax exposes the patient to the risk of an empyema. The same reasoning applies to all pulmonary suppurative diseases in the treatment of which collapse measures have been suggested.

A timely paper by Heaf (120) lays particular stress on the misapplications of pneumothorax treatment both with respect to improper choice of patients as well as with respect to administrative and technical difficulties that are encountered in the course of treatment. The increasing popularity of pneumothorax has led to its adoption by physicians who are not familiar with the course of pulmonary tuberculosis and the complications that may arise during treatment. One should not expose a patient with pulmonary tuberculosis to collapse therapy without weighing carefully the potential risks which the patient incurs. Every time a lung is collapsed by pneumothorax the pleural space becomes the site of a potential empyema. Even after the successful completion of pneumothorax treatment, the reëxpanded lung may become the seat of fibrosis and bronchiectasis or the heart and mediastinal structures may be so dislocated in the thoracic cavity that the patient may suffer considerably as a result of the "cure."

Recent advances in the treatment of pulmonary tuberculosis with collapse measures, particularly in the management of complications that arise in the course of treatment, have not been an unmixed blessing. The phenomenal increase in the last few years in the number of patients treated by collapse measures has reached a stage where in some institutions the treatment is looked upon almost as a specific for the disease. This attitude is deplorable since it is bound to lead physicians to take unwarranted risks with their patients. The mere fact that the prognosis in certain types of pulmonary tuberculosis appears gloomy does not in itself constitute an indication for collapse treatment in a particular instance. Patients are more apt to be made worse than benefited by applying collapse treatment as a measure of last resort.

The occasional success of bilateral collapse treatment has been instrumental to some extent in the employment of pneumothorax in patients with active tuberculous foci in the contralateral lung, This is being done with the hope that spontaneous retrogression will occur in the untreated lung or, if it becomes necessary, bilateral pneumothorax applied. Many physicians will agree with Heaf that this is a dangerous policy to pursue indiscriminately particularly in patients with poor resistance. In such individuals, pneumothorax is more likely to aggravate the disease in the contralateral lung and a secondary pneumothorax will not remedy the situation.

Fibroid pulmonary tuberculosis with thick-walled apical cavities and emphysema of the lower lobes, even if unilateral, is not suited for pneumothorax treatment. This is understandable from the nature of the pathologic process. The condition is most often encountered in individuals past middle age. The symptoms are referable to the emphysema and fibrosis rather than to the tuberculosis. Additional encroachment on an already diminished vital capacity is unwarranted. It stands to reason that pneumothorax should not be employed in the presence of any tuberculous or nontuberculous complication which in itself constitutes a serious disability.

IV. INDUCED PNEUMOTHORAX: APPARATUS; TECHNIQUE; IMMEDIATE RESPONSE TO TREATMENT

The injection of air into the pleural cavity in an attempt to collapse a tuberculous lung is accompanied with surprisingly little operative danger or even discomfort to the patient. Considering the magnitude of the undertaking and the comparative risks associated with other forms of collapse therapy, this in itself has been one of the chief sources of popularity of pneumothorax treatment. There are physicians with many years of experience who claim they have never met a serious accident. In most instances, it is additional proof of the relative innocuousness of the procedure; at times, however, one must give due credit to a kind Providence. The writer has encountered practically all the complications that may arise in the course of pneumothorax treatment, and for this reason has developed considerable respect for the procedure.

It is beyond the province of this review to describe the various types of pneumothorax machines that are in use or to detail the technique of injecting air into the pleural cavity as advocated by different physicians. It is doubtful if either has much to do with the results. The Forlanini apparatus with attached water manometer is as serviceable today as it was at the turn of the present century. Indeed, the original apparatus was reported lately still in use (191). The results from pneumothorax depend primarily on the proper selection of patients, and individualization of treatment rather than on refinements in technique. The contrivance which the writer has been using for a number of years is one similar in construction to the Robinson apparatus (fig. 1).

Two bottles, *B1* and *B2*, with a capacity of slightly more than 1000 cc. each, are mounted on a stand which allows their raising or lowering to any desired level. Bottle *B1*, is graduated from 0 to 1000 cc. downward. Each bottle is fitted with a two-hole rubber stopper and two glass tubes, one short and the other reaching to the bottom of the container. The long glass tubes are connected by rubber tubing, *T1*, so that by raising either bottle its water content, containing a few cubic centimeters of phenol, is displaced into the other. The amount of air expelled from bottle *B2*, through a long, hard-rubber tube *T2*, can be determined by measuring the level to which the water recedes in bottle *B1*. The long tube, *T2*, has a glass tube attachment lightly packed with absorbent cotton which serves as an air filter.

A U-shaped manometer, *M*, (Pilling) is attached to the stand as well as a corrected scale whose centimeter values are doubled, i.e., 0, 2, 4, etc., the 0 mark being at the level of the water meniscus in the center of the scale. The numbering is duplicated above and below the 0 mark. A long, hard-rubber tube, *T3*, is attached to the right arm of the manometer, the latter having bulbous ends which act as over-flow chambers in case the water is accidentally forced out by cough or is sucked up by high negative intrapleural pressure. In addition, tube *T3* has a one-way stop cock, *S1*, the purpose of which will be made clear later. A small glass tube, *W*, is attached near the end of tube *T3* to serve as a safety-window.

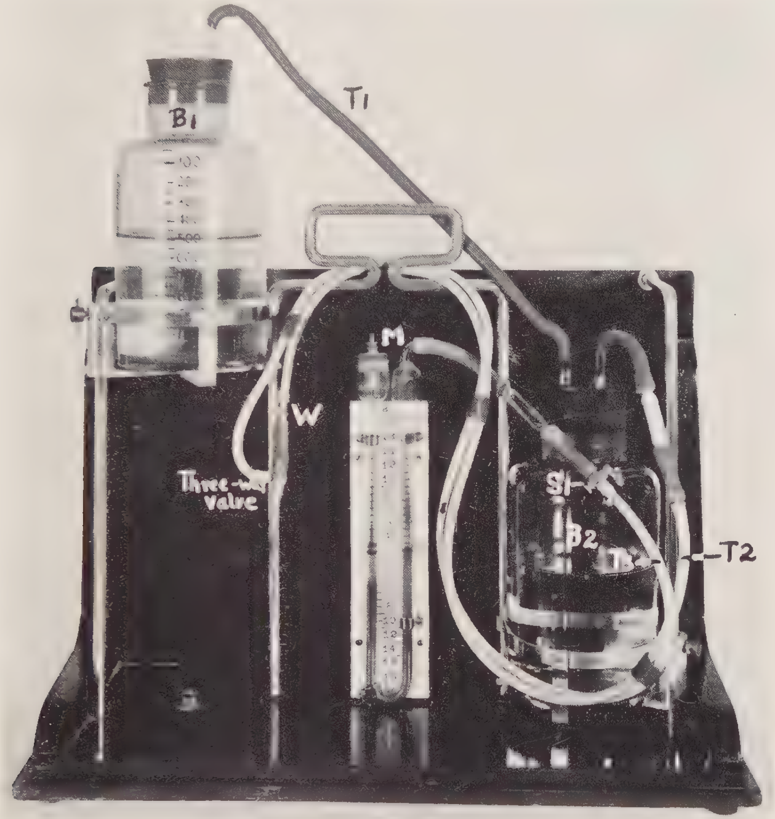

Fig. 1. Pneumothorax Apparatus with Manometer

Tubes *T2* and *T3* are held together by means of several rubber bands. The terminal ends of the tubes are attached to a stop-cock having a three-way valve. One opening serves as a needle adaptor; a second opening allows air-tight communication between the manometer and the needle adaptor; a third opening allows communication between the air bottle and the needle adaptor. As illustrated (fig. 2), by making a quarter turn of the valve to the right, air is allowed to enter the pleural cavity and by keeping the valve head parallel with the manometer tubing, fluctuations are obtained in the manometer. The rapidity of ingress of air and the amplitude of the manometric oscillations can be regulated by partial turns of the valve.

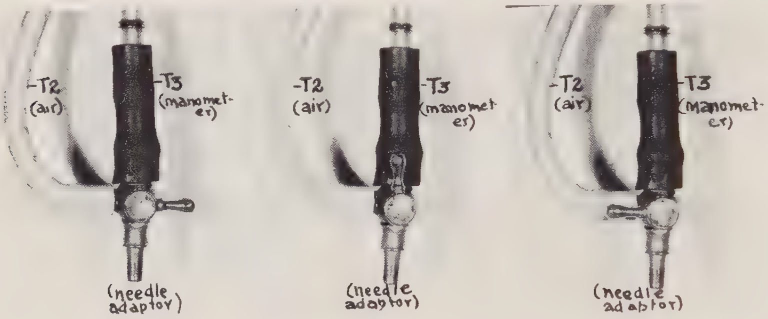

Fig. 2 Fig. 3 Fig. 4

Fig. 2. To Instill Air
Fig. 3. To Obtain Manometric Oscillations
Fig. 4. To Test Air-tightness of Apparatus

A quarter turn of the valve to the left connects the air tube and the manometer tube causing the water meniscus in the manometer to register positive pressure. If the meniscus remains suspended at a constant level, it indicates that there are no leaks in the apparatus. The advantages of a three-way stop-cock are that it enables the operator to instill air or to obtain manometric readings, at will, without removing his hands from the needle. Furthermore, the operation requires no assistance. The stop-cock and adjacent rubber tubings can be sterilized by boiling. The entire apparatus fits into a case and is easily transportable.

The addition of the manometer to Forlanini's apparatus made the instillation of air into the pleural cavity a relatively safe procedure. An upward swing of the column of water in the manometer arm attached to the chest tube, on inspiration, indicates negative intrapleural pressure; a downward swing indicates positive pressure. The difference in the water levels in the two limbs of the manometer registers the total pressure in the pleural cavity. By doubling the value of the manometer scale, corrected pressure readings are obtained by noting the swing of the column of water in one limb of the manometer. The pressure readings vary with the bore of the manometer, the diameter and length of the connecting tubing, the diameter of the needle and the depth of respiration. Slight oscillations in the manometer may be registered if the needle is in the lung substance, in which case the mean pressure oscillations are at zero. If the needle point is in the fascia beneath the costal pleura, slight oscillations may also be obtained. When the bore of the manometer is fairly large, minor oscillations do not register as easily as when the bore is narrow. Free, negative oscillations of appreciable amplitude should be obtained in the manometer before any air is allowed to enter the pleural cavity.

It is essential to have some understanding of the mechanics involved in the respiratory act in order to appreciate the changed status induced by pneumothorax. The visceral and parietal reflections of the pleura are normally in close contact, lubricated by a layer of serous fluid. Any attempt to measure intrapleural pressure is accomplished by allowing the ingress of bubbles of air between the two pleural layers. Such measurements reveal in health negative intrapleural values with the negativity greatest at the end of inspiration and lowest at the end of expiration. The cause for this is quite understandable. With inspiration there is an increase in the circumference of the thorax. This increases the hydraulic traction on the visceral pleura with a resulting increase in intrapleural negativity (10).

The change in intrapleural pressure represents, according to Parodi (197), the difference in the capacity of the pleural cavity and the lung volume. As might be expected, pulmonary condensations cause an increase in the negative pressure while emphysematous states cause a decrease. The intrapleural pressure is zero at birth and reaches maximum in adulthood due to the fact that the thoracic cage enlarges faster than the lungs. Since the pressure in the lungs equals that of the atmosphere, the pressure in the pleural cavity is equivalent to that of the atmosphere less the amount of resistance offered to the intrapulmonic pressure by the elastic elements of the lung. The intrathoracic pressure varies considerably in different individuals, the normal value being a relative term. The latter has been fixed by von Muralt (277) as -10 or -12 cm. water in quiet inspiration and -4 or -2 cm. in quiet expiration. Forced inspiration or expiration, pleural effusion or change in the position of the body alter considerably the values obtained.

The entry of air into the pleural cavity abolishes the pull exerted by the thorax on the lung so that the latter, in the normal state, is able to retract to the hilus. Rightly speaking, therefore, pneumothorax, carried out under negative pressure, is a relaxation rather than a collapse measure. The beneficial effects of the procedure depend primarily on factors intrinsic in the lung rather than in the pneumothorax. In instances where the diseased lung is unable to retract to the hilus, as a result of mechanical interferences, supplementary measures such as the severing of pleural adhesions or diaphragmatic paralysis are often indicated. Even thoracoplasty is basically a relaxation rather than a collapse measure for reasons which cannot be discussed here.

The initial injection of air is usually attempted in the fifth or sixth interspace in the postaxillary or midaxillary line. Some favor other sites. It is preferable to puncture the pleura away from diseased parts of the lung. Fishberg (87) recommends that puncture be made at the site where a pleural friction rub is audible. With the patient lying on the uninvolved side on a small, hard cushion placed under the chest and the upper arm flaccidly outstretched so as to widen the intercostal spaces, the skin is cleansed with tincture of iodine and alcohol and draped with a small sterile towel that has an opening in the center. Some physicians use sterile gloves. The majority simply wash their hands thoroughly and take particular pains to handle the needle with care. A few minims of 2 per cent procaine hydrochloride solution without adrenalin are injected into the skin and the remainder of the anaesthetic is infiltrated into the intercostal muscles and the subpleural fascia. Prior to infiltration the column of water in the manometer arm that is attached to the rubber tube, *T3*, is sucked up some distance and the stop-cock, *S1*, is closed so that the column of water in the manometer remains suspended in the proximal arm.

Following infiltration, an 18 gauge, short-bevelled needle is inserted a short distance into the intercostal space. The needle adaptor of the three-way stop-cock is then attached and the needle is inserted until the pleura is reached. Stop-cock *S1* is opened allowing direct, air-tight communication between the pleural cavity and the manometer. By this means the pleura is entered under negative pressure. When free oscillations are noted in the manometer, the valve of the three-way stop-cock is turned to the right and air is allowed to be sucked in from the air bottle, the height of the column of water in bottles *B1* and *B2* having been previously allowed to settle to the same level. Bottle *B2* is lowered slowly and about 200 cc. of air are allowed to flow into the pleural space, the procedure being checked by frequent manometric readings. For refills a 20 gauge Luer needle is used and the pressure bottle is placed to its full extension height. Five or six inflations are given in the first two weeks at increasing intervals. In most instances anaesthetization of the skin can be dispensed with after the patient becomes accustomed to the procedure.

A free pleural space is not always found and frequently several attempts have to be made before manometric oscillations are obtained. Before repeating the procedure at a new site, the stilet should be inserted into the lumen of the needle since very often the absence of oscillations is caused by an obstruction rather than an adherent pleura. In the writer's experience, failure to find a free pleural space after three or four attempts at different sites is seldom followed by success later. Although there are instances on record of successful induction following numerous attempts, it is problematical whether the resulting pneumothorax is of induced or of traumatic origin. The only way of ascertaining whether the pleural cavity is free or obliterated is by trial and error.

The first few months of pneumothorax inflations constitute the critical period of the treatment. It is in this period that complications are most apt to occur. Furthermore, this period gives an insight as to the probable efficacy or inefficacy of the treatment. The technique of refilling the pleural cavity represents comparatively few problems. Of greater importance are the frequency of refills, the amount of air to be instilled and the general management of the patient. It is advisable in the first few months of treatment to give small refills at frequent intervals. In patients with widespread disease, particularly if symptoms of activity are present, it is desirable to collapse the lung as completely as possible. Refills of 300 or 400 cc. of air, at first twice a week and later once a week or once in ten days, best serve the purpose. Rare instances have been described of so-called "drinking pleura" or "insatiable pneumothorax" (43), requiring large and frequent refills of air. Before such diagnoses are made, it must be first ascertained whether the air is being instilled into the pleural cavity or into a bronchus.

The optimum pressure at which pneumothorax should be maintained varies with the individual patient. Categorically, it can be defined as the lowest pressure needed to obtain a complete collapse of the diseased parts of the lung. It frequently happens, however, that in instances where a complete collapse is desired it is not obtained because of the presence of pleural adhesions and in instances where a complete collapse can be obtained it may not be desired because of the circumscribed nature of the disease. If a satisfactory collapse can be obtained with negative pressure it is unnecessary to increase the pressure. On the other hand, it is poor practice to maintain a pneumothorax under negative pressure that does not collapse a demonstrable cavity unless, of course, widespread adhesions are present. Although the indiscriminate use of pneumothorax at positive pressure, as practiced several decades ago, has rightly been discarded, it would seem that the pendulum has swung too far the other way. There are occasions when an increase in the pressure will collapse a tuberculous cavity without recourse to intrapleural pneumonolysis or paralysis of the diaphragm. On the other hand, the writer has encountered instances where adhesions under tension prevented cavities from closing. By reducing the size of the pneumothorax and relaxing the adhesions, the cavities closed. It is inadvisable to manipulate the pressures in the first few weeks of treatment. The immediate aim should be to rid the patient of symptoms rather than to collapse cavities.

The physical findings during pneumothorax treatment are very misleading. Quite often, a sizable pneumothorax escapes physical detection. The presence of an effusion or pleural adhesions also alters the physical signs. On percussion, one can often demonstrate an area of increased resonance but frequently no change can be elicited in the percussion note. Occasionally, when the mediastinum is displaced, tympany may be elicited over the cardiac area or even on the contralateral side. In the majority of patients, there is suppression of breath sounds but rarely complete absence. In some, one obtains amphoric breath sounds and metallic tinkle but not as often as in instances of spontaneous pneumothorax. Râles and adventitious sounds usually disappear with the establishment of the pneumothorax. Riviere (220) draws attention to the fact that occasionally râles heard over the contralateral side prior to the induction of pneumothorax disappear following the institution of pneumothorax on the affected side. The writer has encountered several instances where râles were elicited for the first time in the untreated lung following the induction of pneumothorax.

For the proper spacing of refills and for gauging the amounts of air to be injected, fluoroscopic examination is indispensable. When radioscopic examination is not immediately available, as when the induction is done in the patient's home, a helpful guide in determining the amount of air to be instilled is the position of the apex beat of the heart. Fluoroscopic examination may reveal the diseased lung to be concentrically collapsed in the region of the hilus or displaced en masse parallel to the mediastinum. Occasionally, the entire lung is pushed upward by a large pocket of air simulating a condition observed following diaphragm paralysis. In most instances, the collapse is uneven, a frequent finding being a collapsed lower lobe and a completely or partially adherent upper lobe. The success of the pneumothorax depends upon its qualitative rather than its quantitative characteristics. A partial pneumothorax may be effective by allowing collapse of the diseased parts of the lung; a larger pneumothorax may be ineffective if the collapse is mainly at the expense of the healthy lobes. The success of the pneumothorax is best judged by the symptoms of the patient, by the persistence or disappearance of cavities, and by the presence or absence of tubercle bacilli in the sputum.

Fluoroscopic examination of the patient frequently reveals instructive findings. Rist (218) has drawn attention to a condition of "heart-flop," occasionally seen in patients receiving pneumothorax on the left side. The left ventricle in such instances discloses an unusual degree of pulsation and the heart as a whole appears to contract in an up-and-down, hammer-like manner. Occasionally, there are present subjective symptoms such as palpitation and a sense of oppression in the precordial region. Sewall (243) detailed studies made by Bronfin who observed the phenomenon of "heart-flop" in 10 of 20 instances receiving pneumothorax on the left side, particularly in the presence of a collapsed lower lobe. The condition was rarely present in patients receiving pneumothorax on the right side. Sewall believed that the unusual mobility of the left heart was due to a lack of support normally offered by the covering lung.

Pendular movements of the entire mediastinum and its contents are occasionally observed on fluoroscopic examination. Marked degrees of mediastinal shifting may occur with each phase of the respiratory cycle without causing symptoms. In some individuals, the mediastinum reveals localized areas of herniation in its "weak spots," described originally by Nitsch (192). The herniation increases in size during expiration and reduces during inspiration. Localized herniations of the mediastinal pleura particularly from left to right occur most often anteriorly at the level between the first and third ribs, the site of the atrophied thymus. In rare instances, herniations occur posteriorly at the level between the fifth and tenth dorsal spines. In the presence of a pleural effusion, the latter herniation may give rise, particularly in children, to a contralateral, paravertebral triangle of dullness (Grocco's sign).

In the production of mediastinal displacements, the distensibility of the mediastinal pleura and the size of the pneumothorax are of more importance than the height of the intrapleural pressure. Herniations of the mediastinum frequently occur in young individuals in the presence of a negative intrapleural pressure and are often absent in instances of spontaneous pneumothorax under positive pressure. In the presence of an inert diaphragm, mediastinal shifting is occasionally accompanied by a paradoxical upward movement of the diaphragm on inspiration (Kienböck phenomenon) (139). Both conditions, as has been pointed out by Stivelman, Hennell and Golembe (253), occur in response to changes in intrathoracic equilibrium. Efforts have been made to correct marked degrees of mediastinal displacement when they interfere with an effective pneumothorax. Some have tried the injection of substances such as gomenol (176) in order to provoke a pleuritis and thereby stiffen the mediastinal pleura. Ascoli (16) recommends a contralateral supporting pneumothorax to which reference will be made later. In some instances an intercurrent pleuritis causes spontaneous fixation of the mediastinum; large effusions often aggravate the condition. Quite often the condition remedies itself in the course of time if an even pneumothorax is maintained under low tension.

A great deal has been written on the mechanism involved in the formation of a selective pneumothorax (26) during treatment of pulmonary tuberculosis by air inflations. The phenomenon is occasionally noted in the presence of a free pleural space and a hypotensive pneumothorax, particularly in monolobar disease. As a result of the reduced volume of the diseased lobe caused by fibrosis and shrinkage, following the induction of pneumothorax, the affected lobe retracts to a greater degree than do the healthy lobes. In instances of exudative pneumonic tuberculosis, the localization of the instilled air over the site of the disease is probably due to the lobular atelectasis present in such lobes. In some instances, the healthy lobes in time become adherent to the chest wall and the pneumothorax becomes encysted over the diseased area. It must be emphasized, however, that a selective pneumothorax cannot be attained through any particular skill on the part of the physician. The determining factors are beyond his control. Once a selective pneumothorax establishes itself and it is desirable to maintain it, the prerequisites are small, frequent refills at a pressure that is slightly negative at the end of expiration.

The writer has encountered four examples of selective pneumothorax of an unusual type. In one patient, a diabetic boy with a tuberculous cavity in the right upper lobe, a selective pneumothorax was obtained over the affected lobe. The treatment was maintained under low tension for about a year and was discontinued intentionally. During the period of treatment, it was noted that the affected lobe underwent complete collapse and occupied the triangular recess formed by the heart and the right leaf of the diaphragm. Simultaneously, the uninvolved upper lobes became enlarged so that they filled the entire hemithorax. The end result, roentgenologically, duplicated the picture of acquired atelectasis occasionally seen in children following bronchopneumonic infections. Similar occurrences were noted in a young woman with a tuberculous process in the right upper lobe, in another young woman with tuberculosis in the left upper lobe and in an aged diabetic woman with an ulcerative tuberculosis in the left lower lobe. In all instances a selective collapse of the affected lobe was obtained and, following discontinuance of treatment, the collapsed lobe remained atelectatic while the healthy lobes filled the remainder of the pleural cavity. It was interesting to note that lipiodol studies, which were done in three patients, revealed no abnormality in the bronchial tree in the first case cited, while two others revealed definite bronchiectasis of the atelectatic lobe, simulating the condition of atelectatic bronchiectasis described by Findlay (85). Lobar dislocation in the course of pneumothorax and coincident enlargement of the healthy lobes was first described by Rossel (223) and since by several others.

The mistake is often made of filming the patient in full inspiration immediately following the initial instillation of air. The film taken in this manner may fail to reveal any air in the pleural cavity. The pneumothorax would have been detected had the film been taken following expiration. Occasionally, after the instillation of air, the outlines of the pulmonary cavities are seen more distinctly. In other instances, the pneumothorax causes the disappearance of annular shadows that had previously been considered intrapulmonary cavities. When films prior to the pneumothorax induction are not available, it is not uncommon to see air pockets on the film simulating intrapulmonary cavities.

Following the induction of pneumothorax, particularly in the treatment of clinically active disease, the symptomatic improvement in the patient's condition is often remarkable. There is a diminution of the fever, a lessening of cough and expectoration and a gradual increase in weight. At times, there occurs an increase in fever or a transitory period of increased cough and expectoration that are attributed to the accelerated absorption of toxic products from the collapsed lung. An initial loss of weight is also occasionally observed and is ascribed by some physicians to mediastinal displacements and, in left-sided pneumothorax, to interference with gastric function. In most instances of successful pneumothorax the symptomatic improvement in the patient's condition is so striking that the treatment of pulmonary tuberculosis by pneumothorax would retain much of its popularity even if its value were limited to the alleviation of distressing symptoms. In the spacing of refills, it is obviously poor practice to be guided by rises in temperature or increase in expectoration. Reinflations should be spaced so as to prevent such occurrences.

With the diminution in expectoration, the tubercle bacilli in the sputum diminish in number and finally disappear. In many instances, when the pneumothorax is fairly complete, the disappearance of tubercle bacilli from the sputum is abrupt. Obviously, in the latter event, there must be a mechanical barrier preventing their expulsion since it is hardly conceivable that their disappearance was due to biological factors. Indeed, tubercle bacilli sometimes reappear following an initial disappearance. The phenomenon is also encountered following thoracoplastic operations. Nasta, Blechmann and Bacanu (188) found that the examination of the gastric contents, by guinea pig inoculations, often gave positive results within the first six months of pneumothorax induction although the sputum failed to reveal tubercle bacilli.

Riviere (220) conveniently divides the period of pneumothorax treatment into three stages: "Disappearance of Symptoms," "Clinical Recovery," and "Anatomical Recovery." During the first stage, which may last a few weeks or months, the patient shows the symptomatic effects of the treatment. During the period of clinical recovery, the patient is up and about, possibly engaged in some work, and continues to receive inflations until the disease becomes anatomically healed. It is difficult to demarcate clinical recovery from anatomical recovery for the reason that the transition is gradual and varies with each patient. It is only by painstaking study of the history and serial roentgenograms and particularly by the patient's response to the treatment that one can arrive at a tentative opinion regarding the status of the disease.

V. INDUCED PNEUMOTHORAX: OPERATIVE COMPLICATIONS

The writer has been repeatedly impressed by the fact that complications in the process of induction or during the course of pneumothorax treatment of pulmonary tuberculosis are particularly apt to occur in the following types of patients: (*a*) In individuals with predominantly fibrotic pleuropulmonary disease that is associated with emphysema. Accidents during the induction of pneumothorax are most often encountered in this group. (*b*) In individuals with hyperacute disease. In these, pleural and pulmonary complications during the early months of treatment are frequently observed. (*c*) In individuals in whom difficulties are encountered in inducing, reinducing or maintaining a successful pneumothorax. When such difficulties are encountered in patients of either of the above groups, the possibility of meeting complications is present to an ever greater degree.

It bears repetition that serious complications, particularly those associated with the operation itself, are unusual in patients in whom the induction of pneumothorax meets clear-cut indications and in whom a successful collapse of the lung is realized. On the other hand, they are not at all infrequent in patients in whom pneumothorax is attempted more with the hope than with the expectation of obtaining good results. The proper selection of patients for pneumothorax is the best preventive against the complications of the treatment. These observations find confirmation in a study of the complications that have arisen in the course of pneumothorax treatment at the Montefiore Hospital and in its country sanatorium.

A. Air embolism

Air embolism is said to occur once in approximately every thousand pneumothorax inflations but there is a wide difference in individual experience with the incidence of this complication. Bruns (40) reported 13 instances of air embolism with 4 deaths in 12,700 pneumothorax inflations, while Burrell (46), in approximately 20,000 pleural punctures, encountered only one fatal instance strongly suggestive of air embolism. The accident has been observed in 5 instances, of which 2 were fatal, in approximately 600 patients treated by pneumothorax at the Montefiore Hospital and in its country sanatorium.

The incidence of this complication cannot be ascertained with any degree of accuracy for the reason that many instances of air embolism are ascribed to pleural shock, a condition which will be discussed later.

The following case report illustrates some of the important clinical features of this complication as well as the conditions that favor its occurrence.

J. N., aged 48, revealed a widely disseminated, nodular tuberculosis in both lungs. Both upper lobes were seeded with fibrotic infiltrations and a small cavity was noted in the right upper lobe. There were small, discrete tubercles in both lower lobes which were considerably emphysematous. The trachea was markedly deviated to the right. Pneumothorax was induced on May 13, 1935. The sixth refill was given on May 30. The initial pressure was $-1+1$ and after the instillation of 200 cc. of air the final pressure remained $-1+1$.

During the inflation the patient complained of a feeling of discomfort. At the conclusion of the inflation, the patient sat up but suddenly became pale, swayed and complained of feeling weak. The pupils were dilated and the eyes turned upward. He was immediately put in the prone position. He vomited a small amount of mucous and gastric juice. In a minute or two he became restless and developed clonic convulsions of the extremities. He had a tendency to lie on the left side. The eyes tended to turn to the right. The pupils reacted very sluggishly to light; the fundi were negative. There was no evidence of paresis or paralysis. Approximately three minutes later, a cyanotic mottling was observed in the skin over the right side of the chest which blanched on pressure. The mottling gradually faded. At first, the patient appeared mentally sluggish and responded poorly to questions but at no time was he disoriented or incoherent. Following intensive stimulative treatment, the patient recovered his mental faculties.

A more detailed examination by neurological consultants revealed the following positive findings: (*a*) left homonymous hemianopsia; (*b*) reflexes all equal with the exception of the left ankle jerk which was hyperactive; (*c*) absent abdominals; (*d*) positive Chadwick on left and equivocal on right; equivocal Babinski on left; (*e*) cranial nerves were all negative, except for the seventh, as noted. It was the impression of the staff that the patient had an air embolus in the right retrolenticular space. The patient made a complete recovery.

A roentgen examination of the chest made shortly afterwards disclosed that at no time did the right lung sustain any collapse although six inflations of air had been given.

The clinical features of air embolism show considerable individual variation. In some, the symptoms are of a mild, fleeting nature; in others they are severe and even fatal. The severity of the accident cannot be correlated with the amount of air injected. Our two fatal instances occurred in patients who had not been given air at the time the accident took place. In both instances, however, a partial pneumothorax was present. The features of air embolism that are most striking are the following: the sudden and violent onset; the appearance of embolic manifestations in various parts of the body; the severe nature of the cardiorespiratory distress and, lastly, the fairly rapid disappearance of symptoms and complete recovery of the patient in most instances. The dramatic sequence of events precludes a detailed examination of the patient even if the physician is in a position to do so. His time is usually occupied with the administration of restorative measures the efficacy of which is questionable.

Occasionally, prodromata appear prior to the seizure. The patient may have a fit of coughing and may expectorate blood. He becomes pale, complains of headache or pain in the chest or he may cry out and say that he feels dizzy and is unable to see things. The respirations soon become deeper and labored, the pulse accelerated, and unconsciousness quickly supervenes. Recovery may take place at this stage or the patient's stupor may become more profound and embolic manifestations appear.

During the height of the seizure one or all of three groups of symptoms characterize the course of events: (*a*) symptoms of cardiorespiratory collapse; (*b*) symptoms referable to central nervous system irritation and (*c*) symptoms referable to peripheral embolic localizations. Particularly noteworthy are the tonic and clonic convulsive movements of the extremities that are sometimes followed by paralyses, the ocular disturbances and occasionally amaurosis, and the cutaneous manifestations of embolization as revealed by areas of cyanotic blotchings or marbling of the skin (278) or pallor of circumscribed areas of the tongue (151). The most characteristic symptoms of air embolism are referable to excitation of the motor areas of the brain but careful observations have revealed that air emboli in the vessels of the heart, kidneys and gastrointestinal tract may also produce recognizable clinical symptoms.[1]

The pathogenesis of air embolism is understandable in its broader phases, as revealed by the researches of Wever (283) and Schlaepfer (240) and the detailed postmortem observations by Siebert (246), Bishop (32), Harris (118a), McCurdy (174) and others. In the individual instance, however, it is most difficult to trace the source or the mechanism of the accident even by those who have had experience with the condition. Schlaepfer directs particular attention to the pathological condition of tissue infiltration and induration in the process of which the blood vessels, especially the veins with their weaker walls, are fixed and remain in a distended position. As a result of fixation in rigid surroundings, the injured vein is unable to collapse. If the site of injury is not distant from a large pulmonary vein under negative pressure, aspiration of air may result. The air is drawn into the left heart and travels by way of the aorta to the brain and other organs. The accident is most apt to occur in patients with fibroid pleuropulmonary tuberculosis associated with emphysema. The blood vessels at the periphery of the lung and in the costal pleura are often dilated and verrucous and vulnerable to the type of injury described by Schlaepfer.

Postmortem examinations in a number of instances in which it was possible to study the viscera immediately after death have revealed instructive findings, elucidating the probable mechanism of the condition. McCurdy's patient was shown to have sustained a needle puncture extending through adherent parietal and visceral pleurae which transfixed a pulmonary vein. Because of the large amount of air found in the right heart and systemic vessels, it was believed that the entire 200 cc. of air which the patient received had been injected into the vein. In the instance reported by Harris, there were present in the right lung areas of tuberculous consolidation and cavitation and thickening of the pleura. There was a perforation in one small cavity and in it a vein whose wall had been torn and in this manner the air had probably gained entrance to the circulation. This patient had received between 5 to 10 cc. of air before the accident occurred.

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[1] The first recorded instance of air embolism to the spinal cord following an attempted pneumothorax induction was recently observed on the tuberculosis wards of the Montefiore Hospital. (A. Wikler, J. Marmor and A. Hurst, J. A. M. A., 1937, **109**, 430.)

In instances where air embolism occurs immediately following chest puncture and prior to any instillation of air, one must hypothecate the possibility that the embolism may have been endogenous and caused by the entry of air from an existing pneumothorax. This possibly explains the accident in two of our patients. Bunta (41) ascribed to endogenous sources five of the sixteen instances of air embolism that occurred at the Chicago Municipal Sanitarium. In view of the possibility that air in the rubber tubing and attachments of the pneumothorax apparatus may be sucked into a vein or, more likely, that air may gain entrance during the process of needling the chest, one can never be certain whether the air embolism is of endogenous or exogenous origin even if air is not knowingly instilled from the bottle. It is doubtful if air embolism arises from traumatized alveoli, a circumstance which would have made the incidence of this complication much greater than it is, considering the large number of pleural and pulmonary punctures that are performed for diagnostic and therapeutic purposes. The rarity of the complication speaks for a set of conditions which is fortunately seldom present at one time in the same individual.

To minimize the danger of air embolism during pneumothorax treatment, the following measures may be mentioned: (*a*) During the induction, particularly, the head of the patient should be at a lower level than that of the body. The importance of this procedure is well illustrated by Schlaepfer's experiments whereby he was able to cause air bubbles to appear in the eye grounds of dogs by changing the position of the animal. (*b*) In view of the fact that the induction offers the greatest risk, one should dispense with too many attempts at finding a free pleural space. A successful pneumothorax is rarely obtained after three or four trials. In most instances a free pleural space, if obtainable, is found at the first chest puncture. (*c*) The site of puncture should be distant from areas of disease. (*d*) To obviate the danger of the ingress of air from the rubber tubing and attachments, the induction can be performed under negative pressure in a manner described in a previous chapter. (*e*) Inasmuch as slight oscillations may be registered in the manometer, if the point of the needle is in a bronchiole or possibly in the subcostal fascia, it is imperative that free oscillations on the negative side be obtained before air is allowed to enter the pleural cavity. The suggestion that a more volatile gas such as nitrogen be used at the initial inflation has received few supporters. (*f*) Before refilling the pleural cavity, the writer has found it a good practice to draw some air with a small syringe. A free communication with an open pleural cavity is ascertained in this manner and if difficulties are encountered or if blood is aspirated, another side is chosen for the injection. (*g*) Notwithstanding the risk that the parietal pleura may become irritated from repeated puncture, it is advisable to use a site within a limited range for reinflation. (*h*) There should be at hand ampoules of adrenalin and caffeine should an emergency arise necessitating their use.

B. Pleural shock (pleural reflex; pleural epilepsy; pleural eclampsia)

In the literature on air embolism and pleural shock it is not uncommon for one physician, after studying the protocols of another, to conclude that the first had been mistaken in his diagnosis. Symptoms which one observer may consider pathognomonic of air embolism may be considered by another equally characteristic of pleural shock. Very often both conditions are considered under the heading of pleural shock or nervous accidents of pneumothorax treatment, thus demonstrating the inadequacy of present-day means of differential diagnosis of the two conditions. Experimentally, nothing conclusive has been ascertained. Both conditions have been found to exist but, too often, one to the complete exclusion of the other. Unquestioned evidence of the occurrence of air embolism in man in a variety of conditions has been obtained by postmortem demonstration of bubbles of air in the brain and in other viscera of the body in patients who have come to section immediately after death. Unfortunately, similar objective findings are not available in the verification of pleural shock although this, of course, does not exclude its existence.

Providing the chest is needled, the mere fact that air is not allowed to enter does not rule out embolism any more than does lack of finding air bubbles in the viscera prove that the patient had died of pleural shock. Neither is the severity of the symptoms a dependable criterion in differential diagnosis although, as a rule, the graver seizures are more apt to be ascribed to air embolism and the milder seizures to pleural shock. In recent years the tendency has been to ascribe to air embolism all nervous complications associated with pneumothorax inflations with the exception of such instances where the likelihood was remote that air had entered the circulation. It is noteworthy in this connection that an instance ascribed by Anson (11) to delayed pleural shock finds its counterpart in an instance (case 4) reported by Hamilton and Rothstein (117) where a delayed accident of an analogous nature is ascribed to air embolism.

From the foregoing remarks it is understandable why the incidence of pleural shock varies widely with different observers and to an even greater degree than does the incidence of air embolism. There is no necessity to dwell further on this phase of the subject. Suffice it to state that, although the nervous complications of pneumothorax treatment occasionally give rise to alarming symptoms and even death, their occurrence should serve to make the physician watchful in his selection of patients and of his technique but they should not deter him from undertaking pneumothorax treatment when the indications call for it. Certainly, the patient should not be told of the potential dangers since nervous accidents are said to occur particularly in apprehensive individuals.

Except for several instances of mild fainting spells, we have not encountered any instances of pleural shock that could not be ascribed to air embolism with the possible exception of the following occurrence: S. L., aged 27, revealed on admission an advanced tuberculous process in the left lung. Pneumothorax was attempted but as soon as oscillations were noted in the manometer and before any air had been allowed to enter, the patient became pale, perspired freely and the pulse became hardly perceptible. He remained conscious. With stimulants, the patient improved but the pulse remained between 60 and 70 for the remainder of the day. Three days later, a second attempt was made and 500 cc. of air were given without difficulty.

The following characteristics have been attributed to pleural shock. It is believed that the condition occurs more often in the presence of a healthy pleura or in patients with relatively favorable forms of pulmonary tuberculosis. The symptoms have a tendency to recur in the same patient, a strong argument against the condition being caused by air embolism. The symptoms are indistinguishable from those of air embolism except that pleural shock is particularly apt to be associated with episodes of pulmonary edema. Cooke (57), who describes instances of air embolism and pleural shock under the latter heading, advances a theory promulgated by Meakins in explanation of the condition. The latter hypothecates that under certain conditions there is established a reflex between the pleura and the pulmonary circulation, the spasm of the pulmonary capillary system leading to a rapid rise in the pressure of the pulmonary circulation and a commensurate decrease in the volume of blood reaching the left heart. The resulting cerebral anemia is responsible for the syncope and unconsciousness that follow. Leuret and his associates (150), on the basis of experimental investigations, conclude that pleural shock is a vasomotor phenomenon that involves particularly the bulbar region of the cerebral cortex. Others are of the belief that pleural shock is a misnomer for air embolism and still others acknowledge the existence of both. The treatment outlined previously for air embolism applies as well to pleural shock.

C. Lung rupture

Although the lung is frequently punctured and occasionally lacerated in the process of finding a free pleural space for the induction of pneumothorax, the accident is seldom followed immediately by serious consequences. Following induction, the patient may expectorate blood or may have a transitory period of tightness in the chest which, in the presence of a larger pneumothorax than can be accounted for by the amount of air injected, suggests that the lung had sustained an injury and additional air had leaked into the pleural cavity. At times, the superimposed pneumothorax is instrumental in bringing about a more effective collapse of the lung than might have been obtained otherwise. Occasionally, a transient pleural effusion appears but, as a rule, no permanent harm results. In other instances, the lung injury is followed by severe pain in the chest, dyspnea, cyanosis, tachycardia, fever and, in rare instances, by symptoms simulating an acute abdominal condition (249). Although the patient may recover from the initial shock, there is the danger of the development of a pyopneumothorax and other serious sequellae.

In view of the fact that symptoms of lung rupture may be entirely lacking or so mild in nature as to escape clinical recognition, the exact incidence of this complication is difficult to ascertain. Sachs (236), in a review of 1145 instances of pneumothorax performed in America up to 1915, found only 10 instances of spontaneous pneumothorax complicating induced pneumothorax. More recently, a careful study by Karan (137) revealed no less than 9 instances of rupture of the lung during the induction of pneumothorax in 70 patients. Were it possible to include the many instances of lung rupture that cannot be verified clinically, it would be found that lung injury is the rule rather than the exception in pneumothorax treatment, particularly at the time of induction.

The literature on the subject of lung rupture in pneumothorax is somewhat confusing by virtue of the fact that few investigators distinguish instances of accidental rupture of the lung caused by needling the chest from those of spontaneous or of tuberculous origin and caused by intrinsic factors. Under the heading of spontaneous pneumothorax all types of lung rupture are included regardless of their pathogenesis. An unusual wealth of material at our disposal permits the following groupings of cases, exclusive of those unassociated with symptoms.

1. *Accidental rupture of the lung, at the time of induction, with immediate symptoms.* The accident is apt to follow repeated attempts at finding a free pleural space, particularly in patients with considerable pulmonary emphysema. Although no air is introduced, roentgen examination may reveal a sizable pneumothorax in the pleural cavity. In others, the accident occurs immediately following the instillation of a few hundred cubic centimeters of air, also, as a rule, when technical difficulties are encountered. At times, the accident causes mild symptoms and pneumothorax can be continued; at other times, particularly in patients in whom air had been introduced, the rupture is followed by a severe reaction that often leads to complications.

2. *Accidental rupture of the lung, at the time of induction, with delayed symptoms.* With few exceptions there is great cardiac and respiratory distress of increasing severity. A fatal termination results in many instances. A valvular type of lung perforation is characteristic of this group of patients.

3. *Rupture of the lung in the course of an established pneumothorax.*

A. In a few individuals the occurrence can be ascribed to a late accident of the treatment if it follows attempts to bring about a more complete collapse of the lung by exerting positive pressure. The rupture may occur in the interval between inflations. It is doubtful, however, if positive pressure inflations alone are sufficient to cause rupture of the lung unless there is present, in addition, an active caseous focus in the lung situated at the base of a pleural adhesion.

B. There is evidence to believe that rupture of the lung occurs occasionally in patients with emphysematous types of pulmonary tuberculosis, the rupture being due to the tearing of an adhesion at its insertion in an emphysematous part of the lung. We have had occasion to see emphysematous blebs projecting from the lung into the pneumothorax space. Rupture of a bleb leading to a spontaneous pneumothorax often follows strain of one sort or another and is not readily followed by infection of the pleural cavity. The initial symptoms, however, may be quite severe and necessitate removal of air.

C. In the majority of instances, the rupture occurs at the site of an active caseous process or cavity adjacent to a pleural adhesion. Study of the clinical course preceding the accident often reveals that the patient had active, febrile disease and that the seizure occurred in the absence of any history of strain, frequently while the patient was at bed rest. This type of tuberculous pneumothorax is almost invariably followed by empyema.

Our material includes a number of instances of lung rupture following cessation of pneumothorax treatment and two instances that occurred on the untreated side. These occurrences, rightly speaking, are complications of pulmonary tuberculosis rather than of pneumothorax treatment.

In most instances, needle puncture of the lung gives rise to a small opening which closes and heals quickly aided by the presence of the pneumothorax. A pleural adhesion may hold open the tear on the surface of the lung and air is forced into the pleural space on cough or strain but is prevented from escaping by the valve action of the pleural tear. This condition speedily gives rise to a tension pneumothorax with greatly increased intrapleural pressure. Extreme degrees of intrathoracic displacements may follow leading to circulatory and respiratory embarrassment. This type of lung rupture is often associated with the seepage of air under the skin, into the mediastinum and into the fascial planes of the chest and back muscles. Occasionally, the tear in the lung becomes organized and an open pneumothorax is established, air being able to enter and leave the pleural space with each respiratory act. The condition results in a "dead" pleural space with a permanent bronchopleural communication.

The treatment of lung rupture is largely preventive and symptomatic. At the time of induction the patient should be instructed not to take deep breaths and to control cough. Many physicians prescribe routinely a narcotic preliminary to the injection. It is best to use a blunt needle with a stilet that does not project beyond the tip. When a superimposed pneumothorax occurs, if the symptoms are of moderate intensity it is advisable not to remove air since the collapse of the lung facilitates the closure of the lung opening. If the dyspnea is distressing, it is imperative to evacuate air on one or more occasions. In extreme instances, particularly in tension pneumothorax, one is forced to institute permanent air drainage. This is best accomplished by attaching a rubber tube to the aspirating needle and by placing the distal end of the tube for an inch or two under water. In this manner air is evacuated and the pleural pressure is equalized. Of course, with a valvular opening this procedure is only a makeshift and is physiologically unsound since it tends to keep the opening in the lung patent. By clamping the tube occasionally and noting the effect on the patient's respirations, one can judge when it is safe to abandon this treatment. As a rule, the immediate distress following lung rupture can be relieved but the ultimate prognosis is poor because of the frequent development of pyopneumothorax and cardiac insufficiency.

D. Surgical emphysema

Subcutaneous emphysema at the site of the chest puncture may follow the use of a large-sized needle particularly if there had been much manipulation or excessive cough during the inflation. The condition is seldom encountered if an 18 or 20 gauge needle is used and if the skin is thoroughly massaged after the needle is withdrawn. Moderate degrees of subcutaneous emphysema are of passing discomfort, the condition being easily controlled by external compression.

Extreme degrees of emphysema with widespread involvement of subcutaneous tissues and occasionally the mediastinum are almost invariably associated with rupture of the lung and the formation of a tension pneumothorax. The air escapes at the site of the needle puncture and quickly spreads over the body. It is inconceivable how an internally closed pneumothorax can give rise to an emphysema of large dimension, particularly one that persists unabated for weeks in spite of heroic attempts at deflation. The emphysema disappears with the healing of the lung perforation.

Fenichel (84) described in detail the mechanism of tension pneumothorax with subcutaneous emphysema in two instances studied at the Montefiore Hospital. One followed aspiration of a pleural effusion, the other followed an attempt at intracardiac injection of adrenalin. He ascribes the development of tension pneumothorax to the expulsion of air from the uninvolved lung following cough and strain. The closed glottis directs the expelled air into the bronchi of the contralateral lung thereby raising the tension in the pneumothorax cavity. Otherwise, it would be difficult to explain how air under atmospheric pressure is able to enter a pleural cavity that is under markedly positive pressure. We recently had occasion to observe the following instance of tension pneumothorax, associated with subcutaneous emphysema, in a child three years of age on the Pediatric Service of the Morrisania City Hospital. It bore out the explanation advanced by von Muralt (277), and confirmed by Fenichel, regarding the mechanism involved in the production of the condition.

M. W., aged 3, was admitted to the Morrisania City Hospital with a pneumonia complicated by empyema. Following thoracotomy, the child improved but, for some reason, it was removed from the hospital with a large collection of air still present in the left pleural cavity. The pneumothorax was incomplete, several adhesions being demonstrable at the base.

On March 26th, 1936, two months after leaving the hospital, the child was readmitted with clinical and roentgen signs of a complete pneumothorax on the left side associated with marked dextrocardia. The child was extremely dyspneic, had a high fever and a very rapid pulse. It was the consensus of opinion that the child had sustained a spontaneous pneumothorax superimposed on the previous postoperative pneumothorax as a result of rupture of an adhesion. An attempt to remove air with a syringe forced the piston out of the barrel. The thoracentesis was followed within 24 hours by subcutaneous emphysema of moderate degree.

Repeated daily and twice daily withdrawals of air ranging in amounts from 1000 to 1200 cc. failed to reveal any change in the size of the pneumothorax. Because of the high tension in the pneumothorax cavity, a mercury Baumanometer was attached and the pressure within the pleural cavity was found to be +20 mm. Hg. Following aspiration of 1000 cc. of air, the pressure dropped to +10 mm. Hg. But as soon as the child began to cry and strain, the pressure returned to +20. Because of the poor condition of the child and the fear that a bronchopneumonia might develop on the right side, an intercostal incision was done and a rubber tube inserted. At operation a small amount of purulent exudate was evacuated. Following the operation, the child's symptoms slowly abated and the empyema increased slightly, the excess being discharged through the operative wound. Apparently, the empyema was associated with fibrinous pleurisy that involved the general pleural cavity and the site of the fistulous opening in the lung, for following the operation serial roentgen examinations revealed a gradual obliteration of the pneumothorax space, a return of the heart and mediastinum to the midline and coincident with the physical and roentgen findings there was steady improvement in the clinical condition of the patient.

Our material includes three instances of generalized emphysema involving the face, neck, chest, abdominal wall and extremities. Each instance was associated with rupture of the lung and a tension pneumothorax following attempts at induction of pneumothorax. One died within 24 hours of asphyxia, very likely as a result of a coexisting mediastinal emphysema that caused strangulation of the large blood vessels at the neck. The other two patients recovered but died shortly thereafter, one of a spontaneous pneumothorax on the contralateral side and the other of advanced pulmonary tuberculosis. The condition of all three was verified at necropsy.

The detection of mediastinal emphysema in patients with widespread subcutaneous emphysema is not easy. The loose subcutaneous tissues at the neck are often markedly puffed and yet the mediastinum may be free from air. Indeed, Ballon and Francis (19) found experimentally that when mediastinal emphysema was marked, subcutaneous emphysema was slight and vice versa. Mediastinal emphysema is characterized by marked dyspnea and cyanosis, symptoms that are lacking in instances of subcutaneous emphysema of the neck unless caused by the tension pneumothorax. The roentgen findings are characteristic. The film reveals lateral bulging of the pleural reflections of the mediastinal septum enclosing an area of rarefaction which may extend to the soft tissues of the neck.

Following lung rupture and tension pneumothorax the air permeates interstitially along the fascial planes and sheaths surrounding the blood vessels of the lung and gains entrance into the mediastinum. The site of lung rupture may be at the base of a pleural adhesion situated at the root of the lung or in the vicinity of an interlobar septum allowing subpleural seepage of air into the mediastinum. Mediastinal emphysema of moderate degree occasionally follows the misplacement of the point of the needle and injury of the interstitial tissue of the lung thereby allowing direct communication with a bronchus without the intermediation of a pneumothorax. We have seen this in one instance. The particular patient, following several unsuccessful attempts at pneumothorax induction, after one attempt expectorated blood while still on the table. The same evening she noted substernal discomfort and increasing bulging and crepitations in the left supraclavicular region, later spreading to both submaxillary and pectoral regions. The presence of mediastinal emphysema was easily demonstrable, both deflections of the pleura being separated by air, but neither fluoroscopic nor roentgen examinations disclosed the presence of a pneumothorax. The patient made an uneventful recovery. In most instances, the needle point is inserted directly into a small bronchus and no untoward effects follow. It has been suggested that air may gain entrance to the mediastinum through acquired or congenital fenestrations of the mediastinal pleura. It is doubtful, however, if this pathway is often implicated.

The treatment of widespread emphysema depends on the causative agent. Opiates are indicated to help splint the chest and to diminish cough since the latter furthers the spread of the emphysema. Tension pneumothorax is treated by deflation. Oxygen may be required to relieve excessive air hunger. Considerable amounts of air can be removed from the subcutaneous tissues by aspiration with a syringe or by multiple superficial incisions of the skin in the pectoral region, but as a rule, such treatment is unsatisfactory. Bourgeois and his associates (34) attempted, in one instance, to cut down by means of an intercostal incision to the site of the rupture and to tamponade the lung. The treatment was successful in terminating an asphyxiating emphysema although the patient died of progressive tuberculosis two weeks later. In an instance reported by Gérard-Marchant (100) the same treatment proved successful. The method has been tried since by several other French physicians.

E. Accidental pneumoperitoneum

Accidental pneumoperitoneum is a rare complication of pneumothorax treatment of pulmonary tuberculosis. The accident is most apt to occur in instances of marked pulmonary fibrosis and shrinkage. The roentgenogram reveals a homogeneous density on the affected side that obscures most of the lung detail as well as the position of the diaphragm. This state of affairs was present in the four instances that came to our observation. Instances have been recorded where the complication was caused as a result of a high diaphragm following phrenic nerve interruption (163). With few exceptions, accidental pneumoperitoneum is associated with unsuccessful attempts at pneumothorax induction or reinduction. It may occur at the initial trial or after a pocket of air had been obtained. Although the entry of air into the peritoneal cavity is due in most instances to the misplacing of the needle point below or through the diaphragm, instances have been described where the observer believed it more likely that there had been a natural communication between the pleural and peritoneal cavities. It may be of interest to describe an illustrative instance of accidental pneumoperitoneum.

S. G., aged 25, entered the Montefiore Hospital with an advanced tuberculosis in the left lung. The roentgenogram revealed a dense opacity from apex to base that obscured the lung detail. Pneumothorax was induced on June 21st, 1927 and 300 cc. of air were instilled. The following day she received another 300 cc. of air and two days later an additional 200 cc. of air. The pressures, at first, were slightly negative but at the third inflation became positive. A roentgenogram, on June 25th, revealed a partial pneumothorax on the left side collapsing the lower part of the lung, the upper lobe being diffusely adherent. Following a fourth injection of 100 cc. of air, pneumothorax was discontinued for the time being. On

July 14, another attempt was made and 600 cc. of air were introduced with surprising ease. A roentgenogram taken on July 18th, showed no air in the pleural cavity but revealed a pneumoperitoneum under both leaves of the diaphragm. The patient had no complaints and the pneumoperitoneum absorbed.

Elrick (81), in 1929, was able to find eleven instances of accidental pneumoperitoneum reported in the literature and described an instance of his own. Since his publication, we have found reports of eight additional instances, exclusive of our own. Undoubtedly many instances are not reported and some are overlooked. There is no record that the accident was ever followed by serious consequences. At most, there is passing discomfort and often the condition is entirely asymptomatic.

F. Other complications

The needling of the chest and the use of a local anaesthetic are occasionally attended by reactions of rather obscure origin which are apparently unrelated to the pneumothorax itself. At times, as in the instances observed by MacKay (161), and in several instances that came to our observation, there appears to be a hypersensitivity to the anaesthetic. The patient develops malaise, slight fever, chest pain, anorexia and generalized grippal symptoms which disappear in the course of twenty-four hours. On the other hand, one is more pressed to explain such reactions in patients who do not receive a local anaesthetic. We have in mind particularly a patient who has been receiving pneumothorax for the past 12 years without an anaesthetic. Following the development of an effusion, one and a half years after the induction he began to experience febrile reactions after every refill. Careful inquiry reveals that he is symptomless the first day, has symptoms during the following day and recovers completely on the third day. The reactions are more severe, but not always, if the intrapleural pressure is considerably raised.

Three additional instances have come to our observation in the Montefiore Hospital Pneumothorax Clinic that presented similar reactions. In each instance the febrile reaction first made its appearance following the development of an effusion and persisted in spite of the diminution or complete disappearance of the effusion. Noteworthy, too, is the fact that in each instance the febrile reaction occurred rather late in the course of pneumothorax treatment, a phenomenon to which Baron and his associates (21) have also drawn attention. Occurrences such as the foregoing have been described by Gilbert (102) and others. The exact mechanism of these so-called "refill reactions" is difficult to explain and involves considerable speculation. Much more understandable are such mishaps as traumatic hemoptysis, the breaking of a needle in the chest or the aspiration of fluid into the chest from an unprotected manometer. We have seen instances of each. Among the rare complications, there have been described instances of injury to the intercostal nerve and blood vessels, the latter giving rise to hemorrhagic pleurisy (143), as well as accidental puncture of the heart (254). Among the immediate postoperative complications may be included occasional instances of aggravation of symptoms particularly following the initial treatments. These include gastric and cardiac upsets as well as increased pulmonary symptoms.

VI. INDUCED PNEUMOTHORAX: PLEURAL AND PULMONARY COMPLICATIONS AND THEIR TREATMENT

Pleural complications arising in the course of pneumothorax treatment of pulmonary tuberculosis depend on the character of the disease that is being treated. One is dealing essentially with a pleuropulmonary disease and any attempt to separate the parietal and visceral layers of the pleura offers opportunities for infection. The incidence of the latter depends on the state of the pleural membrane and the success with which the pneumothorax causes the collapse of subjacent, tuberculous foci. It follows, therefore, that the more active and widespread the disease and the less successful the pneumothorax, the more is one apt to encounter complications, particularly if one persists in maintaining the treatment under such conditions. In this respect, the complications that occur are largely preventable. The pleural complications of pneumothorax treatment of pulmonary tuberculosis have given rise to specialized procedures devised to circumvent their effects and to the growth of thoracic surgery as a whole in the treatment of the disease.

A. Pleural adhesions

Pleural adhesions offer the chief obstacle to the closure of tuberculous cavities by pneumothorax. Experience with large numbers of patients in whom pneumothorax is attempted reveals that in approximately 25 per cent a free pleural space cannot be found or, if one is obtained, the diseased part of the lung is so densely bound by adhesions to the chest wall that the pneumothorax is valueless and has to be abandoned after a short trial. In approximately 50 per cent, the pneumothorax is incomplete and in an appreciable number of these it has to be supplemented with other measures. In the remaining 25 per cent, the pneumothorax is productive of a successful collapse of the lung as judged by the symptoms, the sputum and the roentgen findings.

Corresponding to the site of election of pulmonary tuberculosis, the part of the lung which is in the greatest need of relaxation, between 60 and 75 per cent of pleural adhesions are located in the vicinity of the upper lobe (178). The pleural reaction is most pronounced over the postero-lateral aspect of the lobe, the subscapular region. Thoracoscopic studies by Jacobaeus (130), Maurer (171), Matson (166), Stivers (255) and others have shed considerable light on the physical appearance of the lung and pleural cavity in vivo. Stivers found a marked difference in the appearance of a lung that harbors a tuberculous process of less than two years duration as compared to one that is the seat of disease of longer duration. In the former, particularly in an adolescent, the lung is of smooth consistency, freely movable and pale red or slightly gray in color. Adhesions consist of soft connective tissue which frequently contain small blood vessels. In the latter, the lung is dark blue or bluish gray in color, the surface is rather sclerotic and the fine muscular markings on the inner surface of the chest wall are replaced by dense fibrous structure containing many tortuous blood vessels. The adhesions are organized, cover considerable rib surface and contain many blood vessels. In many instances the lung structure is visibly under tension of adhesive bands. The latter, at their insertion, are often imbedded in areas of caseous or fibrinous exudate. Pulmonary tissue or prolongations of cavities are present in the majority of adhesions.

The treatment of adhesions in pneumothorax has occupied the attention of investigators for many years since their presence constitutes a major cause of failure of the treatment and a source of many of the complications. Delicate adhesions give way early in the course of treatment. Firm adhesions persist and any attempt to stretch them by increasing the intrapleural pressure is accompanied by danger. Of the many methods proposed, intrapleural pneumonolysis, first performed by Jacobaeus in 1913 (131), has received the widest recognition and is being practiced with increasing frequency. Technically, the severance of adhesions by means of a thoracoscope is regarded as the most difficult of all collapse procedures. Fortunately, the results attending successful pneumonolysis are commensurate with the difficulties the operation entails. The literature on the subject is voluminous and only the briefest description will be given here of the operation, its indications and results.

Since 1913, the technique of adhesion cutting has undergone considerable modification and new instruments are constantly being devised to meet specific needs. The cauterization of adhesions by galvanocautery has been supplanted in many quarters by electrosurgical methods and by a combination of cauterization and diathermy. The instrument originally devised by Jacobaeus, along the lines of a cystoscope, and subsequently improved by Unverricht (272), employs one cannula to illuminate the inside of the chest cavity and another to convey the cautery. Later, single cannula systems were introduced by Chandler (54), Davidson (70) and others whereby the illumination and operation are performed through a single chest incision. Many, however, still prefer the original type of instrument because the field of vision is better and because the two systems being interchangeable allow the severance of a larger number of adhesions.

Although the chief indication for adhesion cutting is obviously in instances of uncollapsed cavities, it must be remembered that not all instances of partial pneumothorax are failures. The persistence of tubercle bacilli in the sputum is of greater significance. Pneumonolysis may be indicated in the absence of demonstrable cavitation in the collapsed lung if the sputum is bacilliferous. Furthermore, not all cavities are collapsible even if their adhesions are cut and not all adhesions are responsible for keeping cavities open. Thick-walled cavities or cavities situated in the middle parts of the lung occasionally remain uncollapsed even in the presence of a free pleural space. Increased pressure causes the lung and mediastinum to shift in toto to the contralateral side without affecting the antrum itself. Similar experiences are encountered following a technically successful intrapleural pneumonolysis. On the other hand, it is a recognized fact that cavities may close in the presence of pleural adhesions or following partial, intrapleural pneumonolysis that is technically unsuccessful. Each patient requires a period of careful observation and study. A cavity with considerable discharge or one associated with recurring hemoptysis or recent tuberculosis of the larynx may make the operation more urgent. In any event, it must be emphasized that the mere presence of a cavity and an adhesion is not an indication for intrapleural pneumonolysis. Stereoroentgenograms as well as films in the oblique position should be studied for signs of tension of adhesions on the lung. Exploratory thoracoscopy may be necessary before resorting to adhesion cutting.

It is often difficult to decide whether adhesion cutting or diaphragmatic paralysis or thoracoplasty best answers the patient's needs. It seems to be the opinion of competent observers that intrapleural pneumonolysis should be reserved for instances where the adhesions are fairly accessible and of limited extent. Attempts to cauterize adhesions of wide extent or those having diffuse insertions are contraindicated. Jacobaeus (132) recently expressed himself to the effect that he is now more cautious in the severance of extensive adhesions than formerly. He prefers partial thoracoplasty as the less dangerous operation. Regarding the relative merits of adhesion cutting compared to diaphragmatic paralysis, to which reference will be made later, there is no question that when conditions are suitable the former is the logical method, except in instances of basal adhesions or apical and basal adhesions that suspend the lung parallel to the mediastinum. Although phrenic nerve operations are associated with less risk, pneumonolysis in the hands of experienced surgeons offers better prospects of success. There is no doubt that as the operation of intrapleural pneumonolysis becomes more widely and expertly practiced, less need will be found for phrenic nerve operations as an alternate to adhesion cutting. Each procedure has its individual indications.

From a review of the writings on the subject, it appears that adhesion cutting is indicated in about 10 per cent of pneumothorax patients. There are many who find the operation indicated more often and a few who seldom find occasion for its use. Most physicians are in agreement that intrapleural pneumonolysis should not be attempted during the first three or four months of pneumothorax treatment. By this time thin adhesions will have given way and the pneumothorax will have reached its maximum size. In the meantime, the patient will have improved subjectively and the disease will have reached a state of equilibrium. In view of the fact that the first three months constitutes the critical period of the treatment, cavity closure is best attained by small, frequent refills supplemented by temporary diaphragmatic paralysis if the pneumothorax alone does not suffice.

Among the contraindications, Maurer (171) emphasizes that intrapleural pneumonolysis should be performed with great caution in the presence of evidences of generalization for the reason that pleural complications are very apt to be encountered under these conditions. The presence of disease in the "good" lung, unless extensive, is an indication rather than a contraindication for the operation since an effective collapse of the more actively diseased lung may exert a favorable influence on the contralateral lung. A febrile effusion of any character in the pneumothorax cavity is a contraindication for adhesion cutting because of the danger of empyema and fistula formation. The operation has been performed successfully in the presence of chronic, afebrile effusions.

Moore's (180) review gives the results of intrapleural pneumonolysis and the complications that are encountered. The results of the operation, as judged by the success of the procedure in converting a clinically unsuccessful pneumothorax into a successful one, were as follows: In 1850 collected instances, 75.5 per cent were successful and 24.5 per cent were unsuccessful. On the negative side, 4.5 per cent of the patients were made worse and 1.08 per cent died as a result of the operation. The chief complications that were encountered were due to pleural irritation and to injury of the lung substance. Small, serous exudates were present in 22.5 per cent; large and more persistent exudates, in 8.07 per cent; tuberculous empyemas, in 2.2 per cent and mixed infected empyemas, in 1.8 per cent. Hemorrhage (1.5 per cent) was a prominent complication in the earlier years of the treatment. Surgical emphysema of varying extent is a minor complication but one that accompanies almost every instance of intrapleural pneumonolysis.

A measure that is being used with increasing frequency in the treatment of pulmonary tuberculosis is the temporary or permanent paralysis of the diaphragm by the interruption of the phrenic nerve on the affected side. The therapeutic effects of the procedure cannot be entirely explained by the resulting upward displacement of the diaphragm since good results have been observed in the absence of any appreciable change in its position while no effects have followed a considerable upward displacement. In general, however, the greater the degree of upward displacement the better are the prospects of success. Paralysis of the diaphragm does away with the piston-like action of the muscle and contributes to the general rest and relaxation of the lung. Our discussion will limit itself to the indications of diaphragmatic paralysis as a supplement to pneumothorax treatment.

In conjunction with pneumothorax, phrenic nerve operations have been employed under the following conditions: (*a*) as an auxiliary measure, in the presence of pleural adhesions, in order to obtain a better collapse of the lung: (*b*) as a substitute for an unsuccessful pneumothorax prior to the abandonment of the latter; (*c*) to supplement a successful pneumothorax of long duration prior to discontinuation of treatment; (*d*) in the presence of a chronic effusion with beginning obliteration of the pleural space. It was believed for a time that diaphragmatic paralysis lessened the incidence of pleural effusions and that it lengthened the period between pneumothorax refills but these effects are questioned by most observers.

Diaphragmatic paralysis has been employed with considerable success as an alternate to adhesion cutting in instances where intrapleural pneumonolysis is impracticable. Russell (235), in an analysis of the immediate results in fifty instances of phrenic nerve evulsion, in the control of upper lobe adherent cavities, found that phrenicectomy allowed control of these cavities in 54 per cent of the patients. Slavin (247) likewise obtained closure of adherent upper lobe cavities in 18 of 23 instances following phrenicectomy. In instances where the lung is suspenced by adhesions to the apex and base, paralysis of the diaphragm has been found particularly effective since the procedure removes one of the fixed points and permits better relaxation of the lung (261). Even in instances of uncollapsed, large, rigid, apical cavities Burnand and Francken (44) obtained promising results but in most instances the phrenic nerve operation was a preliminary step to thoracoplasty. For this very reason most surgeons do not approve of employing the procedure in these types of cavities.

The advantages of paralyzing the diaphragm in the presence of adhesions that prevent collapse of lower lobe cavities have been stressed repeatedly, the results being even more striking than in instances of upper lobe cavities. Phrenic nerve interruption abolishes the pull of the diaphragm on the lung and allows a better collapse of the diseased lobe. Davies (72) obtained considerable benefit in a large percentage of his patients in whom phrenicectomy was utilized as an accessory to incomplete pneumothorax particularly when the base of the lung was adherent to the diaphragm. Morgan (182), Anderson (9), Gravesen and Tuxen (110) and others have likewise found lower lobe adherent cavities to offer an excellent indication for diaphragmatic paralysis.

It is often preferable to paralyze the diaphragm as a substitute for an unsuccessful pneumothorax for the reason that the danger of complications is particularly great in the presence of suspended cavities. In spite of frequent refills at positive pressure, upper lobe adherent cavities are in most instances uncontrollable by pneumothorax alone. If cauterization is contraindicated or is unsuccessful and thoracoplasty is not in immediate consideration diaphragmatic paralysis is a good substitute. In some instances, it may still be possible to complete the collapse of the lung by pneumothorax after the diaphragm has been paralyzed but in most instances the operation is eventually followed by thoracoplasty.

When pleural symphysis and expansion of the lung is desired, in the presence of a chronic effusion, many physicians find phrenicectomy of value. We have had occasion to verify this observation at the Montefiore Hospital in a number of instances of tuberculous pyopneumothorax. The patients had arrested pulmonary tuberculosis. By frequent aspiration of pus and air combined with paralysis of the diaphragm it was possible to obliterate the empyema cavity in these patients with little difficulty. Tandon (261) reports that at the Carlo

Forlanini Institute, in Rome, every patient with empyema complicating pneumothorax is treated systematically by paralysis of the diaphragm.

Although most observers do not share the view of Davies (72) that upon the successful completion of pneumothorax treatment a phrenicectomy should be done as a routine, many do believe that in instances of widespread, ulcerative disease that had been subjected to prolonged pneumothorax treatment, resulting in marked reduction in the lung volume and thickening of the pleura, a phrenicectomy is useful. By this means the lung does not have to reëxpand to fill the entire hemithorax and the degree of mediastinal displacement is less marked. The paralyzed diaphragm allows a maximum degree of permanent collapse of the diseased lung to take place. When pneumothorax is applied in the treatment of recent, exudative disease of limited extent, there is no need of a phrenicectomy upon the completion of treatment. Many expanded lungs show such surprisingly little abnormality that a permanently paralyzed diaphragm would hardly be an asset to the patient.

Zadek's (285) original suggestion that every pneumothorax be combined systematically with a phrenicectomy for a time attracted few advocates. Recently, however, Pollock and Forsee (210) voiced a similar opinion. The latter investigators came to the conclusion, on the basis of a detailed study of 60 patients, that phrenic exairesis is indicated in practically every instance of induced pneumothorax. Edwards (80) analyzed the after-histories of 582 patients who had been treated by pneumothorax, of whom 262 also had phrenic nerve operations. He found that the results in the latter group were distinctly superior. He considers phrenicectomy of value in all patients treated by pneumothorax except where the latter had been instituted in the treatment of minimal disease. It should be emphasized that whenever diaphragmatic paralysis is indicated to supplement pneumothorax treatment, the earlier the operation is performed the better are the chances of success since fixation of the diaphragm as a result of pleuritis may nullify the effects of the operation.[2]

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[2] A detailed discussion of phrenic nerve operations in the treatment of pulmonary tuberculosis is to be found in a recent review in MEDICINE, Vol. 16, No. 2, May, 1937, by Arthur H. Aufses of the thoracic surgical staff of the Montefiore Hospital.

Mention may be made of several other methods that have been proposed in the treatment of incomplete pneumothorax. The betterment in the pulmonary collapse that occasionally follows the intercurrence of a serous effusion prompted Triboulet and Sors (270) and Zorzoli (289) to experiment with the artificial provocation of a serositis by injecting irritants into the pleural cavity. A febrile reaction follows the appearance of fluid and the increased intrapleural pressure as well as the fixation of the heart and mediastinum in midline serve in some instances to increase the degree of collapse of the lung. Recently, Bethune (30) described an ingenious method (pleural poudrage) whereby he was able to produce selective pleural symphysis without the formation of fluid. He used an iodized talc powder blown into the pleural cavity with a special blower under the guidance of a thoracoscope. Maurer (172) utilized a 50 per cent solution of glucose for the same purpose. Provocative pleural effusions have been obtained with gomenol and a variety of other chemical and gaseous irritants.

It has been our experience that the chief limitation in the foregoing methods of treating an incomplete pneumothorax is one's inability to predict the intensity of the pleural reaction and the course of ensuing events. Were a procedure, such as the one devised by Bethune, found workable, it might be useful in the occasional instance of lobar tuberculosis treated by pneumothorax or in instances of bilateral, simultaneous pneumothorax that do not fall within the province of intrapleural pneumonolysis but which require additional selective collapse of the diseased part of the lung and conservation of the healthy parts of the lung.

Patients who have an unsuccessful collapse of the lung and an appreciable amount of fluid in the pleural cavity may be helped by teaching them to occupy an extreme Trendelenburg position for variable periods of time in order to utilize the hydrostatic pressure of the fluid on the diseased part of the lung. In one instance in which we tried postural treatment of this nature, a large cavity occupying practically the entire left upper lobe became reduced in size to such an extent that it was later possible to perform a thoracoplasty on that side.

B. Serous effusions

Very few patients pass through pneumothorax treatment without developing a pleural effusion of greater or lesser extent. The incidence of this complication depends on the nature of the disease, the character of the collapse and the period of observation of the patient. Small effusions, barely sufficient to obliterate the costophrenic sinus on roentgen examination, are often disregarded or are overlooked in compilations of statistics on the subject. Such "traces" may amount to as much as two or three hundred cubic centimeters of fluid. Of the patients treated by pneumothorax at the Montefiore Hospital and its country sanatarium, 65 per cent had demonstrable pleural effusions. In 40 per cent, the effusion occupied one-third or more of the pleural cavity. It has been claimed, with justification, that every patient who is treated by pneumothorax develops an effusion at some time or other during the course of treatment.

It is the consensus of opinion that pleural effusions during pneumothorax treatment of pulmonary tuberculosis are with few exceptions tuberculous in origin. Small effusions, particularly those not associated with fever, may be caused by traumatic factors such as the irritation of the gas, or repeated puncture of the pleura or may represent transudates caused by alterations in the blood circulation in the collapsed lung. In the majority of instances, however, the effusion is a true tuberculous pleuritis.

The location and character of the disease are intimately related with the incidence and the severity of effusions occurring during pneumothorax treatment. When the disease is situated subapically or in the mesial parts of the lung, pleural effusions are less common than in instances where the disease is situated subpleurally (251). It has also been observed that acute forms of pulmonary tuberculosis are most often associated with pleurisies while chronic forms of the disease show a lower incidence (199). This applies also to the severity of the pleurisy. The allergic condition of the patient is very likely a contributing factor, as has been shown by the experimental work of Paterson (198).

Pleural effusions occur most often in the early months of pneumothorax treatment when adhesions are being stretched or torn and when active disease in the lung is being compressed. This favors infection of the pleural cavity from tuberculous foci adjacent to or implanted on adhesive bands. In 56 per cent of our patients who revealed fluid, the effusion appeared within the first three months and in 80 per cent, within the first six months of pneumothorax treatment. Naveau (189) and Ford (91) reported an incidence of 76 per cent and 72 per cent respectively, within the first six months of treatment. Bunta (42) supports the statement of van Horne to the effect that pleural effusions occur more often in instances where a large pneumothorax space is present following the use of high pressures. The height of the pressure is probably not the chief element involved. Adhesions can rupture under any degree of intrapleural pressure, particularly, it would seem, when there are sudden and marked vacillations in the pressure as on cough or strain.

Although on routine examination of the fluid bacteria are often not demonstrable, particularly in instances of afebrile effusions, careful bacteriological examinations by Pinner and his associates (207) have revealed the presence of tubercle bacilli in as high as 80 per cent of effusions occurring during pneumothorax treatment of pulmonary tuberculosis. Additional evidence of the tuberculous etiology of these pleural effusions is obtained from the following: In instances of spontaneous pneumothorax of the so-called "simplex" of "idiopathic" variety, pleural effusion is the exception rather than the rule. At most, a small effusion is detected. Kjaergaard (140) rarely found more than the slightest amounts of fluid in such instances. Seldom is the effusion caused by outside contamination as attested by the fact that the complication is relatively infrequent in clinic practice where it is the custom to continue pneumothorax treatment successfully induced in a sanitarium or hospital. Were effusions often caused by extraneous factors they would certainly be found with greater frequency in outpatient treatment.

Effusions of nontuberculous origin are exemplified in the so-called "effusions in vacuo." In this variety, a transudate appears in a previously dry pleural cavity following discontinuation of pneumothorax treatment. Intercurrent nonspecific infections of the lung may also initiate an effusion in the pleural cavity. A rare occurrence is the appearance of an effusion on the untreated side. A number of such instances are on record (201).

Several classifications have been devised to differentiate the several types of pleurisies occurring during pneumothorax treatment of pulmonary tuberculosis. Some stress the clinical, others the roentgenological, bacteriological or cytological characteristics of the effusion. For our purpose it will suffice merely to mention some of the outstanding features of the condition.

The sudden appearance of fever in the early months of pneumothorax treatment almost invariably heralds the development of an effusion in the pleural cavity. Occasionally, the patient experiences prodromal symptoms such as pain in the shoulder or a febrile period. These have been ascribed to dry pleuritic manifestations. In many patients the onset of the effusion is symptomless and remains so throughout its existence. The moderately febrile pleurisies last three or four weeks and gradually subside. In a few, the febrile reaction is severe and is accompanied by cyanosis, dyspnea, increased cough, sweating and other constitutional disturbances. "Hot" pleurisies quickly fill the greater part of the pleural cavity and are apt to cause cardiac embarrassment by displacing the heart and mediastinum to the contralateral side. The fluid assumes a variable height compressing the lung against the mediastinum. Occasionally, there is noted a striking diminution in the density of the lung markings following the appearance of a moderate pleural effusion. The partially collapsed lung presents a homogeneous gray appearance that obscures all lung detail. In others, the pneumothorax is paradoxically opaque in contrast to the translucently collapsed lung. These appearances on the roentgen film are caused by a deposition of fibrin on the parietal and visceral reflections of the pleura. The verification of this has been made possible by thoracoscopic examination (88).

The roentgenogram occasionally reveals homogeneous, circular opacities in the pneumothorax space. They are either single or multiple, sessile or freely movable. The densities make their appearance with the recession of pleural effusions. These so-called fibrin bodies, originally recognized by Fleischner (89) in 1922, have since been described by others (244, 263). In several instances it has been possible to study the nature of these bodies following their removal from the pleural cavity by means of a thoracoscope (116) and also at necropsy (286).

The cytological and bacteriological characteristics of effusions in pneumothorax have been studied by a number of investigators (107, 207). Serous effusions in pneumothorax are exudates with a specific gravity above 1.018 and an albumin content proportional to the degree of inflammation present. Most observers have found, after the subsidence of the acute stage, a lymphocytosis in benign effusions and a preponderance of polymorphonuclear leucocytes in malignant effusions. Gloyne draws attention to the fact that it is often difficult to say where the hydropneumothorax ends and where the pyopneumothorax begins. The significance of his observation has a bearing on prognosis and treatment. It serves to explain why the thinness of the pus is often a prominent feature in the successful treatment of pyopneumothorax by one measure or another.

The need of treatment of clear serous effusions in the course of pneumothorax is determined by the severity and persistence of symptoms and the nature of the underlying disease. Small effusions or afebrile effusions of moderate extent seldom require interference. Even large effusions are best treated at first expectantly. For a time small refills can be given until an equilibrium is established. Later, one or two aspirations and replacements with air may be helpful. Occasionally, following aspiration the fluid absorbs and fails to reaccumulate. A febrile effusion should not be aspirated within the first month or two of its appearance unless it causes undue pressure symptoms or an unusual degree of toxemia. As a rule, there is considerable delay in the rate of absorption of the air and the intrapleural pressure is increased, and these factors serve to maintain or even increase the degree of pulmonary collapse.

In instances of advanced pulmonary tuberculosis that had not sustained a successful collapse of the lung and where the prospects of obtaining a satisfactory collapse are poor, it is often preferable to allow spontaneous absorption of the fluid and air and pleuropulmonary fibrosis to take place. A thoracoplasty may come into consideration later. In patients with a successful collapse of the lung and negative sputum, a voluminous and persistent effusion occurring early in the course of pneumothorax treatment is best aspirated and replaced by air, following the subsidence of acute symptoms. If it occurs late in the course of treatment, it may be advisable to aspirate the fluid and to allow the lung to reëxpand. To insure pulmonary retraction and fibrosis, diaphragmatic paralysis is often indicated. A massive effusion that occurs early in the course of pneumothorax treatment that had been unsuccessful and that causes collapse of the lung and conversion of the sputum is best left alone. The effusion is often "providential" and causes striking improvement in the patient's condition and not infrequently arrest of the disease.

As a rule, energetic treatment of serous effusions in pneumothorax is rarely called for. Frequent aspirations may convert a thin, serous effusion to one of seropurulent or purulent consistency. A pleural effusion in itself in prognostically not of great moment, the primary consideration being the character of the underlying disease. The treatment of pleural effusions cannot be standardized. Each patient presents a different problem. On the whole, the condition calls for conservative handling.

Some physicians (46) claim that patients who develop serous effusions during pneumothorax treatment do as well, if not better, than do those in whom the pleural cavity remains dry. Our own statistical analysis agrees with these observations. The incidence of pleural effusion among our patients in whom the disease became arrested and among those who died was approximately the same, 80 as compared to 78 per cent, respectively. In this respect, however, no better example can be cited to demonstrate the fallacy of statistics in interpreting clinical experience. Far from viewing an effusion with equanimity, in the individual instance, the physician is apt to consider the complication unwelcome, to say the least. The presence of an effusion complicates the handling of the patient, induces premature loss of the pleural space and exposes the pleural cavity to the risk of purulent infection and other serious sequellae.

From the foregoing considerations it is understandable why efforts are made to avoid the occurrence of effusions during pneumothorax treatment of pulmonary tuberculosis. It has been claimed that the incidence of the complication is greatly reduced by refinements in the technique of instilling air (224), by the use of calcium gluconate (209) and by inducing a serositis with the aim of thickening the pleural membrane to render it less porous (273). Since the majority of effusions occurring during pneumothorax treatment are tuberculous in origin and are caused by endogenous infection of the pleura and since they appear early in the course of treatment, the logical preventive is the employment of bed rest during the first three months of pneumothorax treatment or for longer periods if the disease does not respond to the effects of the pneumothorax.

C. Purulent effusions

It is customary to distinguish three types of effusions occurring during pneumothorax treatment of pulmonary tuberculosis: (*a*) serous effusions, (*b*) tuberculous empyemas and (*c*) mixed empyemas. The last mentioned variety is the result of mixed infection with pyogenic organisms and tubercle bacilli. Inasmuch as careful bacteriological studies have revealed the presence of tubercle bacilli in the first as well as the second variety, the distinction between serous effusions and tuberculous empyemas is a gross or quantitative one rather than a bacteriological or a qualitative one. Tuberculous empyemas, in contradistinction to serous effusions, are characterized by a greater turbidity of the fluid, a higher specific gravity, a greater amount of albuminous substances, a more cellular content and usually, but not invariably, a greater abundance of tubercle bacilli.

Purulent effusions during pneumothorax treatment of pulmonary tuberculosis arise from a variety of causes. In the majority of instances, the appearance of pus is caused by rupture of the lung or of an adhesion with resulting infection of the pleural cavity. In others, the empyema is the result of superinfection or a gradual thickening of a preëxisting serous effusion. Under the former condition, a bronchopleural fistula is often created with resulting secondary contamination of the pus. This, however, is not always the case. Conceivably, in some instances, a purulent effusion in the pleural cavity can occur by direct extension of the pulmonary disease, by rupture of a caseous lymph gland into the pleura or by hematogenous or lymphogenous metastasis. It is doubtful, however, if the latter pathways are often implicated. Some observers stress the importance of outside contamination in the formation of pus in the pleural cavity. This has not been our experience.

Because of the difficulty in differentiating the various gradations of serous, seropurulent, purulent and mixed pleural infections, the exact incidence of their respective occurrences is not ascertainable. To a great extent the type of patient treated determines the incidence of the complication. There are physicians who seldom meet with empyemas in their practice. There are others to whom the complication always looms as a dreaded by-product of pneumothorax treatment. Based on large numbers of cases, approximately 10 per cent of patients with advanced pulmonary tuberculosis treated by pneumothorax develop purulent effusions, an incidence borne out by the compiled statistics of Hedblom (121), and by our own figures. The earlier the disease is treated and the more effective the collapse, the less frequent is the complication encountered. The sooner an unsuccessful pneumothorax is abandoned, the less likely will an empyema occur. As might be expected, since pneumothorax is applied more frequently in the treatment of left-sided disease, purulent effusions are more often discovered in the left pleural cavity.

The clinical manifestations of purulent effusions vary widely, depending on etiological, bacteriological and mechanical conditions. Particularly significant is the time element involved in the pus formation. A serous effusion following repeated aspirations may become gradually converted into one of purulent consistency without recognizable symptoms. If due to excessive infection of the pleura or to rupture of the lung, the symptoms are apt to be severe. Toxemia of a marked degree is usually associated with secondary contamination of the pus by aerobic and anaerobic organisms. Clinically there is nothing to distinguish, at the onset, a serous effusion from a tuberculous or a mixed empyema except by thoracentesis.

The immediate need of intervention in instances of purulent effusions developing during pneumothorax treatment of pulmonary tuberculosis, is governed by the symptoms which the patient presents. Regardless of the nature of the empyema, distressing symptoms require evacuation of the pus by thoracentesis. After the patient is made comfortable, treatment of a more lasting character comes into consideration. Indications for the latter are determined by (*a*) the condition of the patient and the state of the contralateral lung; (*b*) the state of the lung underlying the pyopneumothorax and (*c*) the nature of the pus. Certain principles have to be kept in mind lest one jeopardize the patient's chances of recovery by injudicious application of emergency measures.

In view of the fact that secondary infection of tuberculous pus renders the prognosis worse, evacuation of tuberculous pus should not be performed by open drainage until all other measures have proved unavailing. The pus can be aspirated and replaced with decreasing amounts of air leaving the intrapleural pressure negative or, as many physicians prefer, aspiration can be followed by irrigation with physiologic saline solution or the instillation of some disinfecting agent such as Dakin's solution, acriflavin, methylene blue, gentian violet or azochloramid. Riggins and Amberson (213) found gentian violet more efficacious in sterilizing empyemas due to gram-positive aerobes and azochloramid more useful in treating empyemas caused by anaerobic organisms or Gram-negative aerobes. If the empyema is secondarily infected and the patient is toxic, as is often the case, it early becomes necessary to resort to an intercostal incision and drainage and occasionally to rib resection. Following detoxication of the patient, if warranted by subsequent events, these procedures often lead to thoracoplasty of a radical character. In the presence of a bronchopleural fistula, the need of prompt and adequate open drainage is even more urgent since irrigations increase the danger of spreading the infection.

An effort should be made to obliterate or at least to reduce the size of the pyopneumothorax space simultaneously with attempts at evacuation of the pus. If the lung has been collapsed for a year or longer and the sputum has been free from tubercle bacilli, frequent aspirations of pus and air and negative suction drainage may be employed to facilitate expansion of the lung. A preliminary phrenic nerve operation is of great help. If the lung is densely bound down by adhesions or its expansion is not desired because it still harbors active disease, thoracoplasty is indicated, depending on the condition of the patient and the status of the contralateral lung. Here, too, attempts should be made to expand the relatively healthy lower lobes or to draw the mediastinum to the affected side in order to improve the chances of complete obliteration of the pleural space following operation.

No two patients present identical problems and, of necessity, one has to be guided by broad principles rather than fixed formulae. Instances occur, but not many, of malignant empyemas that respond to conservative measures. Indeed, we have seen several instances of purulent effusions that underwent spontaneously serous transformation. On the other hand, there are many instances of relatively benign empyemas that eventually need thoracoplasty to effect a cure. There is no need to cite the many advocates of one or another method of treatment. A major and indefinable element, one that is often disregarded in planning treatment and in evaluating the results of such treatment, is the condition of the patient and the extent and nature of the tuberculous process. Hedblom (122) and Jones and Alexander (136) use a clinical classification of tuberculous empyemas that is most commendable for practical purposes. It takes into consideration the nature of the empyema, whether tuberculous or mixed, and the nature of the pulmonary disease underlying the empyema. The essential features of their plan of treatment have been outlined above. Their combined statistics totalling 213 patients show that a great deal can be done for a condition that is associated with a high mortality if left untreated.

Among the many attributes ascribed to oleothorax, its disinfecting action in tuberculous empyema is prominently mentioned. This method, proposed by Bernou (27) in 1922, and since utilized by many physicians on the continent and in America, involves the instillation of variable quantities of antiseptic oil into the pleural cavity. The majority add 5 or 10 per cent gomenol to either a mineral oil base in the form of paraffine or to a vegetable oil base in the form of olive or Wesson oil. Because of its more rapid absorption, a vegetable oil base is preferred in the treatment of virulent, mixed empyemas. According to Matson (167), the fundamental principles of a disinfection oleothorax are the following: (*a*) complete evacuation of the pus; (*b*) thorough cleansing of the pleural cavity and (*c*) a disinfection oil-bath of the entire pleural cavity. Prior to the establishment of an oleothorax the sensitivity of the pleura is tested with a small quantity of the oil and during instillation particular care is taken not to increase the intrapleural pressure.

Rather conflicting results have been obtained with the use of oleothorax as a disinfecting agent in tuberculous empyemas. Bernou (28), in a later contribution, restricts the use of disinfecting oleothorax to empyemas that are not associated with active disease in the lung. He prefers thoracoplasty for patients in whom the tuberculous lesions are insufficiently compressed and still give signs of activity. In nontoxic, relatively inactive empyemas, the treatment has met with variable degrees of success. In toxic empyemas with mixed infection and in empyemas with bronchopleural fistulas, most observers have found the treatment of no value and in some instances not devoid of complications such as febrile reactions, perforation of the lung, oil embolism, paraffinoma, and fistula formation. Taylor (262) concludes, from his experiences at the Brompton Hospital, that the evidences in favor of oleothorax are strong on paper but that in practice the treatment is of limited value.

D. Pulmonary complications

The presence of tuberculous involvement of greater or lesser extent in the untreated lung is such a commonplace that within certain limits this in itself is not a contraindication to pneumothorax treatment of the more actively diseased lung. In 10 per cent of our patients, at most, was the contralateral lung free from recognizable disease. In 70 per cent there were significant parenchymal tuberculous changes demonstrable in the "good" lung. Matson, Matson and Bisaillon (168) found the contralateral lung "essentially negative" in 23 per cent of their patients. In an analysis of a rather select group, Peters and his associates (200) found the "good" lung involved in two-thirds of the patients. Obviously, the incidence of contralateral involvement in the course of pneumothorax depends on the status of the "good" lung before the institution of the treatment. It is for this reason that an exact incidence of contralateral activation of old disease or progression of new disease is not ascertainable, the figures varying from 2.6 (59) to 36 per cent (219). In any event, the occurrence of contralateral progression of the disease is one of the most serious complications of pneumothorax treatment and accounts for as much as 75 per cent (219) of the total number of fatalities. In approximately half of the patients treated by pneumothorax, contralateral involvements, when they occur, appear within the first six months of treatment (25, 219).

In addition to the problematical status of the untreated lung prior to the induction of pneumothorax there are certain factors referable to the treated lung which bear on the incidence and the prognosis of contralateral tuberculous involvement during pneumothorax treatment. These pertain to the site of the disease, its character, and the type of collapse which the diseased lung sustains. The comparative rarity of contralateral pleural effusions during pneumothorax treatment and the topographic character of contralateral extensions speak for direct intracanalicular spread as the pathway chiefly concerned in the spread of the disease.

In any analysis of large numbers of patients treated by pneumothorax, one is impressed by the frequency with which cross extension occurs from an uncollapsed cavity in the right upper lobe to the apical and lower portions of the left lower lobe. Disease in the left lung, on the other hand, is more apt to spread caudad rather than to the right lung. In their study on aspiration bronchopneumonia in adult phthisis, Landreth and Morlock (147) draw attention to the frequency of axillary involvement of the contralateral lung. In the majority of their patients, aspiration occurred from an initial site in the right lung to the left lung. These pathways of extension of pulmonary tuberculosis have been the subject of studies by Fleischner (90), Bernou (29), Cardis and Joannette (51) and others.

The frequency with which tuberculous involvement occurs in the contralateral lung, particularly in the early months of pneumothorax inflations, depends on the character of the disease prior to the institution of the treatment. The more active the disease, the greater are the risks of contralateral involvement. Pneumothorax is often applied as soon as the diagnosis is made in instances of seemingly unilateral pulmonary tuberculosis. After spread occurs, careful study of the films may reveal that the presumably clear contralateral lung was the seat of an active tuberculosis before the pneumothorax had been induced. The collapse of the diseased lung may have aggravated a smoldering process in the contralateral lung or may have played no part at all in later events. This state of affairs is strikingly brought to one's attention in the occasional instance where the treatment is for some reason temporarily withheld. It is therefore a good practice to have available a recent film before pneumothorax is induced, lest the treatment be applied unknowingly to a patient with bilateral, active disease. As a rule, it can be stated that active pulmonary tuberculosis of any appreciable duration is seldom unilateral by the time pneumothorax is induced and involvement of the "good" lung is essentially a characteristic feature of the disease rather than a complication ascribable to the treatment.

Of paramount importance in the contralateral progression of pulmonary tuberculosis during pneumothorax treatment is the effectiveness of the collapse of the treated lung. This is to be expected since the primary objective of the treatment is the prevention of aspiration of tubercle bacilli to uninvolved parts of the lungs. In the absence of an effective collapse, the greater the amount of expectoration and the richer its bacillary content, the greater are the risks of a "spill-over" into other lobes. This is well illustrated by Terrasse's (264) figures. Among his patients whose cavities remained uncollapsed contralateral disease was observed in 54 per cent as compared to 9 per cent, in the instances where the pneumothorax was successful.

The behavior of activated disease or fresh implantations in the contralateral lung during pneumothorax treatment depends on the morphological characteristics of the disease and the stage of pneumothorax treatment. They serve to explain the seemingly paradoxical situations that are often encountered. The earlier the contralateral involvement appears and the severer the accompanying symptoms, the worse is the outlook. A careful study of our material reveals that considerable information of prognostic value can be gleaned from a study of the clinical course of the disease and the roentgen films in the months immediately preceding the institution of the pneumothorax. In most patients the immediate response of existing tuberculous foci in the untreated lung depends on the character of the disease. The subsequent evolution of these foci depends on the effectiveness of the collapse. In the early months of pneumothorax treatment of febrile, progressive disease, any immediate change in the status of the contralateral lung is apt to be for the worse. With greater effectiveness of the collapse and improvement in the condition of the patient, there is often noted retrogression of the disease in the untreated lung. When pneumothorax is applied initially in the treatment of afebrile, relatively benign disease, existing tuberculous foci in the untreated lung are apt to evidence retrogressive changes immediately.

One cannot promulgate hard and fast rules in the treatment of active disease in the untreated lung occurring during pneumothorax treatment of its fellow. One is guided essentially by the same considerations that motivated the initial institution of the pneumothorax. In addition, one is confronted with two elements of unknown quantity, namely, (*a*) the extent of healing that has taken place in the treated lung and (*b*) the altered status of the patient from a prognostic point of view. The subject will be discussed more fully in a later chapter.

In many European clinics, gold preparations (sanocrysin, krysolgan, crisalbine, etc.) have been found of value in the treatment of active foci occurring in the contralateral lung during pneumothorax treatment of pulmonary tuberculosis. With few noteworthy exceptions (7, 39, 124), this treatment has received little attention in America. The modus operandi of gold preparations in pulmonary tuberculosis is not well understood. Although sanocrysin, the preparation originally introduced by Møllgaard (179), has practically no bactericidal action on the tubercle bacillus in vitro, it is claimed, that, in vivo, the drug stimulates in some manner the defensive mechanism of the body. A number of observers have correlated the action of the drug with the reticulo-endothelial system. Others have ascribed its beneficial action to the shock effects of the drug. Clinically, sanocrysin has been found of value in facilitating retrogressive changes in recent, exudative types of pulmonary tuberculosis but not in fibroid disease. The most detailed report on the subject in America is that by Henrichsen and Sweany (124). These investigators claim, as do many others, that in conjunction with collapse treatment sanocrysin is indicated as a supportive treatment when there is beginning spread to the other side or when there is need to clear up a slight involvement in one lung preparatory to the collapse of the other. On the other hand, carefully controlled studies over a period of years by Peters and Short (202) and Guinard (112) appear equally convincing to the effect that no particular benefit can be ascribed to sanocrysin, its value being largely of a psychotherapeutic nature.

In addition to occasional nontuberculous pulmonary infections to which both the treated and untreated lungs are subject, at times, the pneumothorax itself gives rise in the treated lung to perifocal inflammatory reactions, spread of the disease with increase in the size of the cavities and pulmonary hemorrhage. These complications, in most instances, are associated with incomplete collapse of the lung. Their treatment resolves itself into making the pneumothorax more effective. This is particularly true in overcoming pulmonary hemorrhage occurring during pneumothorax treatment.

VII. INDUCED PNEUMOTHORAX: GENERAL MANAGEMENT AND TERMINATION OF TREATMENT

During the first three months of pneumothorax inflations, the critical period of the treatment, the main objective is to rid the patient of symptoms and to improve his nutrition and well-being. At the same time, an effort is made to bring about a satisfactory collapse of the lung by judicious spacing of refills at optimum pressures. The first three months encompass most of the potential complications that have been described in the previous chapters. If, at the end of this period, the pneumothorax is incomplete, supplementary measures, chiefly intrapleural pneumonolysis or phrenic nerve operations, come into consideration. By the end of the first six months, the pneumothorax is effective in most patients in whom a successful outcome is to be expected. Periodic instillation of air until the disease is considered anatomically healed is all that is necessary. At this stage of the treatment, unless there are contraindications, some form of thoracoplasty is substituted if the pneumothorax is unsuccessful.

From the foregoing considerations it is evident that the first three to six months of pneumothorax treatment are best spent in an institution that is equipped for all types of collapse treatment. Here the patient's needs can be studied and an adequate collapse of the lung established. It carries the patient over the most hazardous period of the treatment. The patient learns by observation and from personal experience many essential facts about tuberculosis and its treatment and, what is equally important, he becomes mentally prepared for the various collapse measures that fate may have in store for him.

During the period of pneumothorax establishment, which comprises about two weeks, it is advisable to keep the patient in bed with or without bathroom privileges depending on the individual's adaptability to bed confinement. Later, the amount of freedom accorded the patient depends on his clinical response to the treatment. In the presence of symptoms of activity, bed rest is indispensable for as long a period as may be necessary to bring the disease to quiescence. Patients with initially "cold" disease can be given bathroom privileges a day or two after the initial inflation and can be allowed to sit up for several hours a day as soon as the pneumothorax is fairly well established. The patient's activities are reduced on the day pneumothorax is given. In a previous chapter, we enumerated the criteria by which one gauges the patient's response to the treatment. The extent of his activities are regulated accordingly. It bears repetition that at the outset one is concerned with the behavior of the vital signs rather than with the character of the collapse. The two do not necessarily coincide.

The patient becomes quickly reconciled to the prospect of living for a time with "one lung." In most instances, particularly if the treatment brought about symptomatic improvement, the patient is not particularly distressed by this knowledge. Following the initial period of treatment, preferably spent in a sanatorium where the effectiveness of the pneumothorax is made clinically secure, the patient is ready to continue treatment in the vicinity of his home, either in a pneumothorax clinic or in a physician's office. Upon his return home, the effectiveness of the pneumothorax is put to a severe test. A period of adjustment begins during which the individual gradually resumes his former mode of living and in time engages in some type of work. Tuberculosis sanatoria number among their employees many individuals who receive pneumothorax and there are many also in cities who receive refills periodically and earn a livelihood for themselves and their families.

During the past six years we have had an opportunity to observe the progress of the working pneumothorax patient in the Pneumothorax Clinic of the Montefiore Hospital. It may be of interest to cite briefly some of our impressions of ambulatory pneumothorax treatment.

From October, 1930, to July, 1936, more than 3000 refills have been given to 124 individuals, including 13 who had complicating diabetes mellitus. Of the entire number, about one-half are or have been engaged in some sort of work, either at the Altro Shops, conducted by the Committee for the Care of Jewish Tuberculous, or in various manual, clerical and business ventures. A number of the younger patients resumed studies that had been interrupted by their illness. Many of the women are occupied with household duties. An additional number are able to work but are unable to find employment. The supervised type of work obtainable at the Altro Shops is ideal for the patient recently discharged from the sanatorium who is receiving pneumothorax. There is great need for similar types of institutions.

Every patient treated in the clinic had been at one time or another an inmate of the tuberculosis wards of the Montefiore Hospital or of its country sanatorium. The treatment in the clinic is a continuation of the pneumothorax, in most instances, begun in these institutions. By frequent consultation with staff physicians, with the medical department of the Altro Shops and by presentation of perplexing problems to the weekly division conferences, an effort is made to conduct the clinic as an integral unit of the Tuberculosis Division rather than as an out-patient department of a hospital in the usual sense or the term. Yet, in spite of careful supervision, fluoroscopic screening at every refill and frequent roentgenographic examinations, it is a difficult matter to individualize treatment in a clinic. Every so often one finds a patient's mediastinum displaced to an undesirable degree or the pneumothorax space contracting because of improper spacing of refills or of insufficient pleural pressures. One has to be at all times on guard lest the procedure disintegrate to a routine of injecting needles and instilling air.

Some of the patients receive refills every week particularly when first admitted to the clinic. Later, the interval is lengthened to two, three and even four weeks. Quite often a patient expecting a treatment is advised, after fluoroscopic examination, to return at some later date. It is preferable to maintain an even and sustained collapse of the lung and not to allow wide excursions between refills. Selectivity on the part of the pneumothorax is largely a matter of chance but whenever possible in such instances an effort is made to keep the intrapleural pressure negative to facilitate this type of collapse. At each visit, the patient's temperature, pulse and weight are recorded and, when indicated, the sputum and blood are examined. All sputa and gastric lavages are examined routinely by the antiformin method and often by guinea pig inoculation.

The patients with complicating diabetes are under the supervision of an experienced physician who regulates their diet and insulin requirements. Every two or three months the patient's status is reviewed and inquiry is made into his mode of living and his work. A representative of the social service department coöperates with the physicians in ironing out individual problems. This type of care, as can be readily seen, places a limit on the number of individuals that can be handled adequately in a pneumothorax clinic.

In 90 per cent of the patients, pneumothorax had been instituted six months or more prior to their admission to the pneumothorax clinic. Nine of every ten patients come with a successful collapse of the lung and almost invariably without constitutional symptoms. At the present time 82 patients are receiving pneumothorax treatment. Of this number, one, a tuberculous diabetic, has tubercle bacilli in the sputum and another has tubercle bacilli in the gastric lavage. The remainder do not reveal tubercle bacilli on repeated antiformin examinations. These are primarily the reasons why with few exceptions, the patients do well and complications are seldom encountered. As a rule, patients come to the clinic with an excess of weight and in the first few months of ambulatory treatment the majority lose weight. This does not affect their well-being in any way. We have treated patients who on admission were underweight and who gained weight while working. It is to be expected that some of the surplus weight which patients amass under restricted activities should be lost when the individual returns to work.

In spite of the fact that the individual is working, has to travel after treatment and is no longer in the shelter of an institution, pneumothorax refills can be given for years without serious mishaps. The only operative complications encountered were the breaking of a needle under the skin in one patient and small, traumatic hemoptyses in two others. In none did serious results follow. The incidence of complications during the course of ambulatory pneumothorax treatment in patients with a successful collapse of the lung is probably no greater than in institutional pneumothorax treatment. Small effusions are often present when the patient first appears for the continuation of treatment. Occasionally they appear and disappear during the ensuing months. Effusions of appreciable size are relatively infrequent. Empyemas are a rarity although it should be noted that there is seldom an occasion to perform a chest aspiration and an occasional benign, purulent effusion may have escaped attention. Several patients were admitted with mild forms of laryngeal tuberculosis. The writer does not recall an instance that occurred while the patient was receiving pneumothorax treatment in the clinic. These observations are in striking contrast to one's experience in institutional practice during the first six months of pneumothorax treatment. Patients treated in a well-supervised clinic represent a group in whom pneumothorax reveals its most gratifying features both to the patient and to the physician.

This brings up the matter of the indications for discontinuation of air inflations, a relatively neglected side of pneumothorax treatment. Fortunately for the physician's peace of mind, one does not meet with the problem as often as might be expected considering the large number of individuals who are undergoing the treatment. In an analysis of our own material and that of others, we estimate that 10 to 15 per cent of patients in whom pneumothorax is induced manage to maintain their pneumothorax space for as long as two years, the minimum duration of treatment which the majority of physicians consider essential for anatomic healing. Inasmuch as in only about half of this group is the treatment discontinued intentionally (194), it must be evident that in well over 90 per cent of patients pneumothorax is discontinued involuntarily for reasons which will be discussed presently. Of approximately 600 patients treated by pneumothorax at the Montefiore Hospital and in its country sanatorium, in no more than thirty instances was the treatment discontinued intentionally, nearly all within the past six years since the establishment of the Pneumothorax Clinic.

In the issue of *La Vie Médicale* of November, 1932 (145), the entire number is devoted to a symposium expressing the opinions of 28 prominent French and Swiss phthisiologists with reference to the problem how long should pneumothorax be maintained. Some believe that two years are sufficient. Others believe that the treatment should be maintained indefinitely. Many refuse to commit themselves to a stipulated period claiming that the duration of pneumothorax treatment has to be solved on individual grounds in which social and economic factors play an important rôle. The time limits set by these physicians and the reasons given for their respective views have been voiced by others both in America and on the continent. Those who claim that pneumothorax of as short a duration as two or three months suffices in the treatment of recent, exudative types of pulmonary tuberculosis have more faith in the vis medicatrix naturae than in the pneumothorax. Those who advocate pneumothorax for life apparently have little faith in either. To the patient afflicted with pulmonary tuberculosis the prospect of lifelong treatment is not a very encouraging one. To the student of tuberculosis the lack of precise knowledge on the subject shows that there is still much to be learned about the disease.

As guiding principles in the intentional discontinuation of pneumothorax treatment the following may be mentioned: The indications for discontinuation of treatment should be consistent with the indications that motivated the induction of the pneumothorax. The more urgent the initial indications, and the more widespread the disease, the longer should the collapse be maintained. Patients who had no tubercle bacilli in the sputum and no demonstrable cavity formation can be treated for relatively short periods. Of particular significance is the time element involved in the rate of the disappearance of the bacilli from the sputum. The earlier the sputum becomes free from the bacilli the better are the prospects of obtaining permanent arrest of the disease (275). The duration of effectiveness of the pneumothorax, in addition to the clinical and roentgen findings, is judged by the length of time tubercle bacilli had not been demonstrable in the sputum although even this factor cannot be taken on its face value. Not infrequently a cavity may be visualized on the film in the absence of tubercle bacilli in the sputum. Obviously, complete cavity closure must be realized before the pneumothorax can be considered successful. The indications for intentional discontinuation of pneumothorax treatment would seem quite obvious. Yet, it is a difficult matter to translate the various factors mentioned into chronologic terms.

Of particular importance, and one on which we place considerable reliance, is the course of events during the maintenance of pneumothorax treatment. Patients who respond favorably early in the course of treatment and, what is more significant, continue uninterruptedly to do well throughout the period of treatment and while at work are better risks for intentional discontinuation of pneumothorax than are patients whose course of treatment is interrupted by one or more exacerbations of the disease. In the latter event, regardless of the effectiveness of the collapse, the duration of effective treatment should be measured from the time of the occurrence of the last relapse.

Before pneumothorax is discontinued intentionally it is taken for granted that the clinical, roentgenological and laboratory tests are in keeping with the status of arrested disease. The physician who is acquainted with the entire history of the patient's illness is in the best position to decide when the treatment should be terminated. The shortest period we have allowed to elapse before discontinuing pneumothorax treatment has been seven months; the longest period, five years. The average length of time has been slightly above three years. At the present time, we are inclined to believe that in patients with advanced, ulcerative pulmonary tuberculosis, three to four years is an average length of time an effective pneumothorax should be maintained. In instances of recent, subapical disease with cavity formation and tubercle bacilli in the sputum an effective pneumothorax of eighteen months to two years would seem a suitable period of treatment. It is very likely that pneumothorax can be applied with safety for considerably shorter periods as attested by the many instances of arrest of disease following forced abandonment of treatment of relatively short duration. For obvious reasons, however, the treatment cannot be discontinued intentionally on the basis of a scientific formula.

We agree with Packard (194) that an unwarranted fear has been engendered by physicians who advocate prolonged pneumothorax treatment because of the potential hazards incurred in allowing a lung, once the seat of advanced tuberculosis, to reëxpand. Such fears are more imaginary than real; certainly, they are not based on a critical study of the subject. A tuberculous lung that has been collapsed successfully for a year or longer, if necessity arises, can be allowed to reëxpand without undue trepidation. Where one has a choice in the matter, a longer period of treatment is advisable as an insurance, of doubtful dependability, that the disease will remain under control after the treatment is discontinued. In the individual instance, however, the optimum duration of pneumothorax treatment is a matter of sheer guess.

By the time one decides to discontinue pneumothorax treatment, most patients are receiving small refills of air every three or four weeks or even at longer intervals. The lung is by this time partially expanded and careful study of serial roentgen films with respect to the site and the character of the initial disease gives a fair inkling of the character of the healing process. This is correlated with repeated examinations of the sputum. Except in the occasional instance, in which absorption of air takes place rapidly, it is unnecessary, at this stage, to diminish further the amounts of air injected. Refills are discontinued and the patient is advised to return for periodic physical and roentgen examinations. It usually takes two or three months and often much longer before the lung expands to the chest wall. This permits resumption of the pneumothorax if found necessary. Unfortunately, in practice, relapse is apt to manifest itself months or even years after the lung has fully expanded and, in most instances, after pleural obliteration has taken place. We have reason to believe, however, that when pneumothorax is discontinued intentionally, in the presence of a free pleural space, symphysis of the pleural layers is less apt to occur. The speed with which the air is absorbed from the pleural cavity depends on the physiological state of the pleura and the amount of shrinkage and fibrosis that has taken place in the lung. In uncomplicated cases, we have never encountered an instance where the pneumothorax failed to absorb leaving a "dead space" in the pleural cavity.

There are certain disadvantages associated with pneumothorax treatment that is unnecessarily prolonged either because the patient refuses to allow the pneumothorax to be discontinued or because the physician is loath to assume the responsibility of terminating the treatment. The least important consideration is the ordeal of repeated pleural puncture. By the end of three or four years of pneumothorax treatment an inflation once in three or four weeks usually suffices to keep the lung collapsed. Very often in such instances the diminution in the pleural space is due to mediastinal displacement rather than to expansion of the lung. We have at the present time under observation a patient who has had a right-sided pneumothorax for the past twelve years. Whenever he feels "out of gas," which happens every six or eight weeks, he comes to the clinic for an inflation. Prior to the instillation of air fluoroscopic examination reveals the lung only slightly expanded but together with the displacement of the mediastinum to the affected side it appears as if little air is present in the pleural cavity. The initial pressure is markedly negative and after an instillation of 150 to 200 cc. of air, the pressure becomes positive and an excellent pneumothorax is again visualized with the mediastinum back in midline. We have seen less striking instances of a similar nature in others. In the instance cited, the patient refuses to abandon the treatment and to undergo a phrenicectomy which we feel is indicated in this type of case.

As long as a free pleural space exists, there are always hazards of pleural infection. Furthermore, prolonged pneumothorax causes fibrosis in the lung and pleural thickening that is injurious to the healthy parts of the pulmonary parenchyma. Should it become necessary at a later date to collapse the contralateral lung, this factor might become an important consideration. Although a "dead space" rarely results unless a bronchopleural fistula is present, when a lung is collapsed for a long time and is allowed to expand, considerable mediastinal displacement is apt to take place, which may progress to an embarrassing degree. This is particularly true in instances of right-sided pneumothorax. Then, too, the symptoms that occasionally make their appearance following expansion of the lung and to which reference will be made later are particularly apt to be annoying in instances of prolonged pneumothorax treatment.

As was indicated previously, in approximately 90 per cent of instances air inflations have to be abandoned involuntarily for one reason or another. The causes of premature discontinuation of pneumothorax during the first six months of treatment are to be found in the various operative, pleural and pulmonary complications that have been described in previous chapters. Once the individual weathers the first six months, the chances of maintaining a successful pneumothorax become better with the passage of time. Some of the causes of premature abandonment of pneumothorax in the later stages of treatment are found in the following: obliterative pleuritis with or without associated effusion; contraction of the pleural space not necessarily associated with pleural symphisis; local recrudescence or generalizations of the disease (particularly frequent in patients with diabetes); nontuberculous disease of major character; economic reasons; irresponsibility on the part of the patient; marriage and gestation.

Loss of the pleural space is a frequent byproduct of pleuritis which may or may not be associated with fluid in the chest. In most instances pneumothorax is abandoned early in the course of treatment because the collapse of the lung is frustrated by the presence of adhesions or a massive effusion occurs in the pleural cavity. Occasionally, one is forced to abandon a successful pneumothorax after a short period of treatment because of a tendency on the part of the lung to creep out to the chest wall, in spite of frequent refills at positive pressure. The process may occur in the absence of demonstrable effusion although as a rule some fibrinous exudate is present. Obliterative pleuritis does not necessarily preclude arrest of the disease. On the contrary, it may prove salutary particularly in instances in which the pneumothorax was ineffective in fibrosing small ulcerative lesions. The intense pleural reaction is often associated with a fibrotic reaction in the lung parenchyma and the end result, although not dependable, is occasionally surprisingly good.

Efforts have been made to control premature loss of the pleural space by converting the pneumothorax to an oleothorax. So-called "inhibition oleothorax," "maintenance oleothorax" or "oleothorax antisymphysaire" have been used for some time on the continent and lately in America. From a careful review of the writings on the subject and from his own meager experience, the writer is not particularly impressed with the merits of the procedure. Oleothorax has been heralded as a cure for too many of the complications of pneumothorax treatment to fail to arouse one's skepticism regarding its panacean qualities. That several hundred cubic centimeters of a mixture of oil and antiseptic can be instilled into the pleural cavity in a patient with a successful pneumothorax is not sufficient in itself to recommend the treatment. An adequate number of observations on the condition of patients who have maintained an oleothorax for several years is still lacking. Until then final judgment must be held in abeyance.

Considerable discussion has been devoted to the indications of pherenicectomy as a final "coup de grâce" to pneumothorax treatment of pulmonary tuberculosis. On the whole, the writer is inclined to believe that as a refinement of pneumothorax treatment the procedure has a limited field of applicability. Patients who have had a successful pneumothorax for two or three years do not need a supplementary phrenicectomy to insure arrest of the disease. If the pneumothorax has failed, paralysis of the diaphragm will not materially alter the results. In such instances, paralysis of the diaphragm is only apt to interfere with the proper aeration of the healthy lower lobes. In unsuccessful instances, the patient may need a functioning diaphragm should thoracoplasty come into consideration later. The writer has seen a number of patients, however, in whom phrenicectomy would very likely have prevented the marked degree of mediastinal displacements that followed the abandonment of pneumothorax treatment that had been maintained for an unduly long time.

Among the noteworthy symptoms following reëxpansion of the lung are the following. There may occur some loss of weight, an increase in cough and expectoration and slight dyspnea on exertion. Varying with the extent of the mediastinal, cardiac or diaphragmatic displacements, there may appear palpitation and gastric upsets, the latter being a more prominent feature of left-sided pneumothorax treatment. A drawing sensation in the chest, particularly on change of weather, and fleeting pains are frequent complaints. Marked degrees of dextrocardia may evoke considerable tachycardia and dyspnea.

The findings elicited on physical examination of the chest are in keeping with the degree of pleuropulmonary fibrosis, emphysema and bronchiectasis that may be present. Asymmetry of the thorax and scoliosis occur more often following absorption of a hydropneumothorax although they may be evident to some degree even during the course of pneumothorax treatment. The findings on percussion and auscultation run the entire range of physical diagnostic signs, even cavitary breathing being audible in patients with displacements of the trachea to one or the other side. The reader is referred to two excellent monographs, one by de Weck (73) and the other by Véran (275), in which are described in detail the condition of patients with lungs reëxpanded following pneumothorax treatment. There is no necessity to dwell on the subject here.

The foregoing considerations relative to the duration of pneumothorax treatment bring up another vexing problem, namely, relapse in pulmonary tuberculosis. It is beyond the scope of this review to deal adequately with this subject but insofar as it relates to pneumothorax treatment one should not lose sight of the fact that, regardless of the care exercised in the choice of patients for intentional discontinuation of pneumothorax in certain individuals the disease will activate in situ or will appear in the contralateral lung or in distant organs, irrespective of the length of time the treatment had been maintained. Relapse in certain instances is unavoidable and is inevitable. It is the price the victim pays to a recrudescent disease. The physician's tendency to lengthen the treatment period every time such an occurrence takes place only serves to confuse the issues and prevents a solution of the problem. In a recent study on prognosis in arrested pulmonary tuberculosis, Spector (248) found that relapse occurred with the same frequency in patients treated by pneumothorax as in patients treated by bed rest alone.

Before closing the chapter, it is in order to discuss briefly the subject of reëstablishment of pneumothorax after it had been abandoned. In the majority of patients pleural obliteration takes place. Several years ago the writer had occasion to collect from the literature the reports of a number of instances and to cite an instance of his own where it was possible to reëstablish a satisfactory pneumothorax after a lapse of years (232). Since then he has met with similar experiences and citations in the literature. In some of the instances reported, the interval was rather short without there being definite evidence that the original pneumothorax had been completely absorbed; or else, only a small amount of air was injected, the second pneumothorax being soon abandoned. In others, it appears that the reinduction was simply a substitution of air for an existing effusion. However, the number of successful attempts are sufficiently impressive to warrant an attempt at reinduction whenever the indication arises. The shifting of the heart and mediastinum to the affected side may be due to pulmonary fibrosis and atelectasis without there being concomitant pleural symphysis. The only way of ascertaining whether the pleural space is free or obliterated is by trial and error.

Laboratory aids

It is beyond the province of this review to describe the many laboratory tests that have been found useful in estimating the clinical condition of the patient, his need of treatment and the results of such treatment. In the utilization of pneumothorax there are two practical tests that are recognized by many physicians as superior to all others. One is the examination of the sputum; the other is the determination of the velocity of erythrocyte sedimentation. In conjunction with the clinical and roentgenological findings, these two tests offer helpful information on the local and constitutional balance of the patient.

The disappearance of tubercle bacilli from the sputum following pneumothorax induction is a major test of the efficacy of the treatment in view of the fact that it is most difficult to ascertain the exact status of the lung from physical and roentgen examinations alone. If tubercle bacilli are present in the sputum, the treatment has failed to meet one of its main objectives. Regardless of whether or not the tubercle bacilli are reduced in number or whether or not they may be originating in the untreated lung, their persistence indicates that the disease has not been brought under arrest. The patient may feel greatly improved as a result of the treatment and even able to work. It has been shown that the mere reduction in the number of bacilli expectorated lengthens materially the patient's life (113). Yet the patient is still clinically tuberculous. Certainly, one has no right to advocate a major surgical procedure for therapeutic purposes if there is not a reasonable chance that the operation will render the sputum free from tubercle bacilli. It is essential, however, that the criteria are specified by which the results of the sputum examination are determined. Pinner and Wooley (208) were able to demonstrate tubercle bacilli by culture and inoculation methods in about half of sputum specimens that had been found "negative" on repeated smears and concentrations.

The writer has been jolted on several occasions by the finding of tubercle bacilli in the sputum many months after a presumably successful pneumothorax had been discontinued in individuals with clinical and roentgen evidence compatible with arrested pulmonary tuberculosis. One is at a loss as to the best plan to follow in such instances. Of necessity, one adopts a policy of "watchful waiting" with the hope that subsequent examinations of the sputum would fail to reveal tubercle bacilli. The latter usually proves to be the case, nevertheless the experience gives the physician considerable food for thought and the patient cause for worry. Following an otherwise successful pneumothorax, the persistence of tubercle bacilli in the sputum calls for bronchoscopic examination of the bronchial mucosa. Tuberculous bronchial ulcerations are not uncommon.

Recent studies by Sayé (239) and by Bergeron and Mézière (24) indicate that the occasional presence of tubercle bacilli in the sputum of patients with clinically arrested pulmonary tuberculosis is not a rare occurrence. Indeed, Coryllos and Ornstein (65) consider it problematic whether a patient with pulmonary tuberculosis treated by collapse measures can ever become bacilli free, bacteriologically speaking. In evaluating their results, they depend on the examination of the sputum or the gastric lavage by concentration methods. The problem is being studied at present at the Montefiore Hospital.

Of the many tests proposed for the determination of constitutional activity in tuberculosis, the blood sedimentation test has received the widest recognition. In instances where the diagnosis is not in question, the test is of considerable prognostic value in estimating the patient's need of treatment and his response to it. In general, the results with so-called activity tests in tuberculosis, when compared simultaneously, are approximately the same regardless of whether the formed or the unformed elements of the blood are utilized (231). There is considerable difference, however, in the ease with which they can be performed and their adaptability to clinical use. In the writer's experience the blood sedimentation test is the most useful one, an opinion shared by many others.

The technical performance of the test is a matter of common knowledge and need not be described here. In the vast majority of patients the sedimentation readings agree with the clinical findings so that in most instances the value of the test lies in its objectiveness rather than in the additional information it gives. A rapidly sedimenting column of red blood cells indicates active disease and is comparable to the presence of fever in its prognostic significance. In some instances there is an increase in the settling velocity of the blood in the absence of fever in which case the former is the more reliable indicator of the condition of the patient, provided extraneous factors do not interfere with the accuracy of the sedimentation values. The sedimentation test is of value in following the course of pulmonary tuberculosis under the effects of collapse treatment. It often registers impending complications before the appearance of symptoms. It is useful at the termination of treatment and during the succeeding months.

VIII. BILATERAL PNEUMOTHORAX TREATMENT OF PULMONARY TUBERCULOSIS

Following the introduction of pneumothorax, it was thought that the measure was applicable to only a small percentage of patients with pulmonary tuberculosis. This was due to two rigid restrictions which Forlanini had imposed on the treatment, namely, unilaterality of the disease and complete collapse of the affected lung. It was not long, however, before physicians came to the realization that the classical indications for pneumothorax treatment were too narrow and not in keeping with clinical experience. Satisfactory results were obtained in patients in whom only a partial collapse of the lung could be realized as well as in patients who had tuberculous changes demonstrable in the "good" lung.

Among the first to take exception to Forlanini's views was Ascoli (15). This investigator, in 1912, drew attention to the value of intentional, partial collapse of the lung, at low-tension (optimal pressure pneumothorax), in contradistinction to high pressure or compression pneumothorax then in vogue. Shortly thereafter Morgan (183) published a significant contribution on the value of hypotensive pneumothorax. His clinical and experimental observations were enlarged upon by Gwerder (115), who dwelt on the relaxation effects of hypotensive pneumothorax, and by Barlow and Kramer (20), who paid particular attention to the selective action of low-tension, partial pneumothorax. The application of bilateral pneumothorax to patients with bilateral pulmonary tuberculosis was a natural outgrowth of the foregoing contributions.

From 1915 to 1925, bilateral pneumothorax treatment of pulmonary tuberculosis slowly gained recognition and was practiced in a few institutions. In the past decade, with the growth of collapse therapy in general, bilateral pneumothorax has become widely accepted as a valuable method of treatment of the disease. In a recent survey (259), a committee of the American Sanatorium Association reported that, on a given day, no less than 372 patients were being treated in 61

American institutions by bilateral pneumothorax, 5.1 per cent of all the patients undergoing pneumothorax treatment. Of late, the treatment of bilateral pulmonary tuberculosis has availed itself not only of pneumothorax but of every conceivable combination of collapse measures: pneumothorax on one side and diaphragmatic paralysis, oleothorax, extrapleural pneumonolysis or thoracoplasty on the other; bilateral extrapleural pneumonolysis; bilateral diaphragmatic paralysis and even bilateral thoracoplasty. Bilateral pneumothorax has received the most extensive trial and with the increasing use of intrapleural pneumonolysis offers the most fruitful results. The following pages will be devoted to a discussion of this form of treatment.

1. Alternating, bilateral pneumothorax

Bilateral pneumothorax can be applied alternately to each lung on successive occasions or simultaneously. Alternating pneumothorax was utilized by Forlanini (94) in 1911, in the treatment of two patients with pulmonary tuberculosis who, after having been treated by pneumothorax on one side, later required pneumothorax on the other. According to Gravesen (111), Saugman, as early as 1908, had occasion to use alternating pneumothorax in a number of instances. With the increasing use of pneumothorax treatment of pulmonary tuberculosis there has been a corresponding increase in the number of individuals who require alternating pneumothorax treatment as a result of late activation of the disease in the previously untreated lung.

Alternating pneumothorax comes into consideration under one or two conditions. A patient with unilateral pulmonary tuberculosis is carried successfully through a period of pneumothorax treatment. Months or years following the discontinuation of treatment, an active tuberculous process appears in the previously untreated lung and recourse is again made to pneumothorax. Or else a patient with predominantly unilateral pulmonary tuberculosis, while undergoing pneumothorax treatment, sustains an activation of a dormant tuberculous process in the contralateral lung. If the primary pneumothorax had been effective for several years and had apparently not been responsible for the contralateral activation, pneumothorax is induced on the contralateral side. After a variable period of simultaneous, bilateral pneumothorax, the primary pneumothorax is allowed to absorb and pneumothorax treatment is continued on the newly applied side. Rapid progression of the disease in the newly involved lung may necessitate extraction of the primary pneumothorax, particularly if the lung has been under prolonged compression.

No greater significance can be ascribed to the first type of alternating pneumothorax than if the disease had become active in situ and pneumothorax had to be reinduced. The second variety, however, presents several problems. If the secondary tuberculous localization occurs in a previously healthy lung it may well be that the primary disease was not entirely healed and may have been the source of the new implantation. Under such circumstances it is injudicious to discontinue the primary pneumothorax. The problem is much easier of solution if the secondary involvement is demonstrably an activation of a preëxisting focus and the initial pneumothorax had apparently been successful in arresting the disease in the lung. In the later event, it is preferable to treat solely the lung evidencing the recent activation of the disease. Involvement of the "good" lung early in the course of pneumothorax treatment is best treated by bilateral, simultaneous pneumothorax, regardless of the apparent efficacy of the primary pneumothorax or the pathogenetic character of the new involvement.

2. *Simultaneous, bilateral pneumothorax*

Bilateral simultaneous treatment of pulmonary tuberculosis by pneumothorax is also applicable to two major groups of patients. It finds its greatest use in patients who early in the course of pneumothorax treatment experience an activation of the disease in the contralateral lung. In a lesser number of instances an active tuberculosis is present at the outset in both lungs, which appears amenable to bilateral, simultaneous pneumothorax treatment. The institution of pneumothorax simultaneously on both sides involves several considerations of which the most important is the proper choice of patients. Although individuals with bilateral pulmonary tuberculosis constitute the largest group of patients, comparatively few present the necessary indications for bilateral collapse treatment. It is hardly necessary to state that the mere application of a collapse measure does not constitute treatment, unless the measure is successful. As yet, the attempts greatly outnumber the finished products.

Activation of the disease in the "good" lung, occurring as a complication of pneumothorax treatment, provides the most frequent indication for bilateral pneumothorax treatment. The time interval between the respective applications of pneumothorax to the two sides may vary from a few weeks to several years. The later in the course of pneumothorax treatment bilateralization occurs, the better is the outlook. Indeed, late activation in situ in the untreated lung in instances where a successful pneumothorax had been maintained on the contralateral side does not necessarily call for a second pneumothorax. Quite often such an exacerbation, if unaccompanied by significant symptoms or febrile reaction, retrogresses spontaneously with bed rest. When spread occurs to a previously uninvolved lung early in the treatment, particularly when symptoms of clinical activity are present, it is advisable to induce pneumothorax immediately on the contralateral side. The two pneumothoraces may act synergistically as occurred in several of our patients.

Bilateral simultaneous pneumothorax, as a primary objective, is utilized under the following conditions:

a. Advanced, ulcerative tuberculosis in one lung and recent disease of limited extent in the contralateral lung: Patients who present this type of tuberculosis were for many years considered beyond the range of collapse treatment for the reason that active tuberculosis in the contralateral lung was held a contraindication to collapse therapy. The availability of bilateral, simultaneous pneumothorax has enlarged to some extent the field of unilateral pneumothorax. The more involved side is treated first and, occasionally, following a successful pneumothorax, the disease in the contralateral lung retrogresses spontaneously. In most instances, however, the presence of a significant degree of involvement in the contralateral lung calls sooner or later for a pneumothorax on that side also.

b. Recent, isolated cavities in both upper lobes: Among others, Frischbier (97) and Dahlstedt (69) have found this type of pulmonary tuberculosis amenable to bilateral simultaneous pneumothorax. The monolobar character of the disease and, not infrequently, the selective nature of the pneumothorax render this type of tuberculosis suitable for bilateral treatment. The writer has observed on several occasions an analogous tendency towards selective collapse on the part of the diseased lobes in both lungs. It suggests the possibility that certain individuals possess to an unusual degree the elements that contribute to this phenomenon.

c. Small, multiple cavities in both upper lobes of the "punched-out" variety or nodular disseminations in both upper lobes with slight degrees of cavitation: These types of pulmonary tuberculosis, presumably of hematogenous origin, have been found by Sachs and Hoth (237) and Steinbach (250), at the Montefiore Hospital, to be amenable occasionally to bilateral pneumothorax treatment.

d. Among the less frequent indications for bilateral, simultaneous pneumothorax may be listed the following: (*a*) Uncontrollable hemoptysis in patients with an apparently successful collapse of the more involved side (148); (*b*) Mediastinal and cardiac displacements, in which case a contralateral, supporting pneumothorax has been advocated (16); (*c*) As a prophylactic measure following pregnancy (242); (*d*) In the treatment of pulmonary tuberculosis in children (13).

In the utilization of bilateral simultaneous pneumothorax no hard and fast rule can be drawn respecting which side should be treated first and the time interval that should be allowed to elapse between the application of the treatment to the two sides. Usually, the treatment is instituted first on the more diseased side and by the time a successful pneumothorax is established several months elapse before the treatment is applied to the contralateral side. The more progressive the disease, the earlier one attempts pneumothorax on the contralateral side. Whenever possible, the establishment of the primary pneumothorax should be completed before one embarks on the second. As was mentioned previously, occasionally the second pneumothorax is not needed.

Selectivity on the part of the pneumothorax is of utmost importance for its simultaneous, bilateral application. In view of the fact that adequate function of the uninvolved lobes is a prerequisite, the selective localization of the pneumothorax over the site of the disease is necessary not only to render the treatment mechanically effective but to render it functionally bearable. For this reason, adhesions in the pleural cavity, although they may not interfere with the success of the pneumothorax, may need severance in order to decrease the degree of collapse of the uninvolved lobes. Intrapleural pneumonolysis, and to a lesser degree diaphragmatic paralysis, are indispensable measures for the proper conduct of bilateral pneumothorax treatment. There are on record many instances where adhesions have been severed successfully on both sides. For detailed information on the subject the reader is referred to recent publications by Coryllos and Ornstein (65), Corsello and Bruckheimer (62) and Mattill and Kinsella (170).

The contraindications to bilateral simultaneous pneumothorax treatment of pulmonary tuberculosis have to do primarily with the extent and character of the disease and the clinical condition of the patient. Among the former may be mentioned progressive, bronchopneumonic disseminations; fibroid tuberculosis with emphysema, and severe tuberculous complications in the larynx, intestines, kidneys or other organs. Patients who are acutely ill are not suited for the treatment. Particular note has to be made of the patient's cardic and respiratory functions. Individuals with tachycardia and noticeable dyspnea and cyanosis are poor risks. Although from a functional standpoint one-tenth of the lung volume may suffice to carry on oxygenation, it is hazardous to approach anywhere near this limit in practice. The very fact that bilateral pulmonary tuberculosis is associated with a poor prognosis does not in itself constitute a valid reason for applying bilateral collapse measures. Indeed, the more advanced the disease and the worse the prognosis, the more discriminating should one be in utilizing bilateral simultaneous pneumothorax. There is no justification in applying the treatment simply because the patient still has a healthy lobe left. One cannot dissipate the fact that for every individual whose disease becomes arrested with bilateral simultaneous pneumothorax, a much larger number are not helped or are made worse by the treatment.

The induction of pneumothorax on the second side calls for small refills at negative pressure and at longer intervals than is the case with the primary pneumothorax. It is advisable to allow the lung initially collapsed to reëxpand partly before inducing pneumothorax on the contralateral side. Following Liebermeister's (152) observations to the effect that bilateral simultaneous pneumothorax should not be attempted if the vital capacity of the patient is less than 2500 cc. of air, a considerable literature appeared on the subject. It is the consensus of opinion at the present time that unless the vital capacity is greatly induced (less than 1500 cc. of air) there is no appreciable risk of anoxemia or pulmonary insufficiency. Many physicians place greater reliance on the patient's symptoms than on vital capacity determinations. The surprising lack of dyspnea and cyanosis is probably due to the fact, as pointed out by Campbell (49), that the amount of tidal air is little compromised by the treatment. The loss of respiratory capacity is chiefly at the expense of the patient's residual air. With each respiratory cycle, the patient practically renews his supply of air. Although there is much to recommend the instillation of air into both pleural cavities at a single session, in practice, moderate degrees of mediastinal displacements are disregarded and pneumothorax is administered on each side consecutively. From the foregoing remarks it is evident that bilateral simultaneous pneumothorax requires considerable experience on the part of the physician and close observation of the patient. Although the procedure, successfully established in a sanatorium or a hospital, can be continued in a clinic or in a physician's office, the treatment is preferably conducted in an institution until the disease in one lung has undergone healing and the pneumothorax on that side discontinued.

The complications that may arise in the course of bilateral, simultaneous pneumothorax are naturally more frequent and, when they occur, more serious than is the case with unilateral pneumothorax treatment. The chief complications are the development of serous and purulent effusions and rupture of the lung (45, 67). It has been remarked that serous effusions are encountered less often than might be expected due to the greater care exercised in maintaining the pneumothorax at low tension. The second pneumothorax is usually applied to the less involved side where fewer adhesions are encountered and this is probably a contributing element in the relatively low incidence of effusions. The occurrence of a superimposed pneumothorax as a result of rupture of the lung is a much-feared complication. Additional complications that are occasionally encountered are repeated hemoptyses, progression of the disease, pulmonary and cardiac insufficiency. To a considerable degree complications can be avoided by discontinuing pneumothorax as soon as it becomes apparent that the patient is not being benefited by the treatment.

The results that have been obtained from bilateral simultaneous pneumothorax treatment of pulmonary tuberculosis are inconclusive for the reason that the treatment is a relatively late development and has been applied to comparatively few individuals. Many reports deal with isolated instances. Most of the results that have been reported deal with the immediate, symptomatic improvement of the patient or the sputum findings with the lungs still under collapse. To what extent the patient will be permanently benefited by the treatment after it is discontinued is problematical. Coulaud (67) expresses a belief, which is shared by others, that if a satisfactory collapse of both lungs is not realized, a cure is seldom obtained. His statistical study dealing with 116 patients treated by bilateral simultaneous pneumothorax includes durable results in 39 instances. Most observers, however, have not been as fortunate, their successful end-results ranging from 10 to 20 per cent (159, 222).

Pneumothorax and contralateral surgical procedures

A natural outgrowth of bilateral pneumothorax treatment of pulmonary tuberculosis has been the application of pneumothorax on one side and diaphragmatic paralysis or thoracoplasty or both on the other side. These procedures are usually tried following unsuccessful pneumothorax. Occasionally, phrenic nerve interruption is used in preference to pneumothorax on the less involved side, particularly in the presence of lower lobe disease. In 1927, Borchardt and his associates (33) reported 8 instances treated by pneumothorax and contralateral phrenic nerve operations. Since then, the combination has been tried by a number of other physicians. Most observers claim that although the combined treatment is without danger, it is difficult to ascertain in the individual instance the real value of the phrenic nerve operation.

Ameuille (8) appears to have been the first to treat bilateral pulmonary tuberculosis by pneumothorax on one side and thoracoplasty on the other. This combination has been used, in instances of successful pneumothorax on one side, as a substitute for an unsuccessful pneumothorax on the other. Jessen (135), who tried the combined method in three patients, believes that pneumothorax and contralateral thoracoplasty represent the limit in the way of mechanical collapse that can be utilized in the treatment of bilateral pulmonary tuberculosis. Occasionally, pneumothorax is applied in instances of contralateral activation of the disease following thoracoplastic operations.

When pneumothorax and thoracoplasty are combined, an effort is made to maintain a small, selective pneumothorax and to perform a partial thoracoplasty. Many patients, however, have undergone complete thoracoplasty in the presence of quite an extensive pneumothorax. The surgical procedure is accomplished in multiple stages during which a minimum amount of air is maintained in the pneumothorax cavity. According to Pollock (211), patients with vital capacity as low as 40 per cent of normal should experience little respiratory difficulty. He did not encounter a single operative death among 12 patients treated by pneumothorax and contralateral thoracoplasty. Since most reports deal with few instances and the treatment has been practiced for a short time, it is premature to evaluate the results.

IX. PNEUMOTHORAX TREATMENT OF PULMONARY TUBERCULOSIS: RESULTS AND THEIR SIGNIFICANCE

The value of pneumothorax in the treatment of pulmonary tuberculosis is seldom defined by any two observers in the same terms. When similar terms are used, they often refer to different types of patients. In the absence of comparable definitions, therefore, it might be expected that wide discrepancies should occur in the results reported by different investigators. This is true to some extent when one compares the results in small numbers of patients, or recent results, with those obtained fifteen or twenty years ago. But when compilations are made of large numbers of patients treated within recent years, the percentages of positive and negative results show surprisingly little variation. In substance, one finds that about one-third of the patients are clinically "cured," that is, able to work and without tubercle bacilli in the sputum; about one-third are more or less improved and about one-third are unchanged, worse or dead. The significance of present-day treatment of pulmonary tuberculosis by pneumothorax does not lie in the results obtained but in the tremendous increase in the number of patients subjected to the treatment. Instead of devoting much space, therefore, to statistics, it might be more profitable to discuss some of the factors that contribute to the results. The following are the most significant: (*a*) the character of the disease; (*b*) the status of the contralateral lung; (*c*) the effectiveness of the collapse; and (*d*) the period of observation of the patient following cessation of treatment.

Pulmonary tuberculosis is a chronic disease of variable duration, at times progressing and incapacitating the individual, at other times retrogressing, during which intervals the individual feels comfortable and often able to engage in some useful occupation. Such extreme variations in the life cycle of a disease make it very difficult to judge the results from treatment. One often questions, or is questioned, whether the patient might not have done as well without the particular treatment, a thought probably prompted by the realization that patients often fail to respond to seemingly adequate treatment. Gloyne (106) and Cummins (68) have stressed the importance of taking into account the "constitutional balance" of the patient in evaluating the results from treatment. The course of pulmonary tuberculosis of the acute variety differs considerably from that of the chronic variety both as regards the relative prognosis, if left untreated, and the results obtained, if treated. Cummins points out that "many claims for success with 'new' treatments have, as their only foundation, the large measure of acquired resistance that goes with the recrudescent type of phthisis."

The writer has made a careful study of the protocols of the pneumothorax-treated patients at the Montefiore Hospital and in its country sanatorium, many of the patients having been under his personal supervision, in an effort to correlate the course of pulmonary tuberculosis with the results obtained from the treatment. The following observations summarize his impressions:

A prominent feature of the successful outcome of pneumothorax treatment is the frequency with which the disease shows evidence of spontaneous healing prior to the institution of treatment. Although the immediate outlook appears better in instances of active, progressive disease, the end results over a period of years are better in patients showing a greater degree of chronicity.

In the treatment of pulmonary tuberculosis by pneumothorax, the constitutional balance of the patient, as expressed in the temperature, is of major prognostic import. Irrespective of the stage, duration or character of the disease, the prognosis is twice as good in patients who are afebrile prior to the institution of the treatment. Similar opinions have been expressed regarding the significance of the pulse-rate (78, 256).

Although hemorrhage presents a frequent indication for the institution of pneumothorax, in itself blood spitting is of minor prognostic significance. More important is the gain or loss of weight prior to the induction of pneumothorax when the individual is at bed rest. Of our patients who gained weight, almost three times as many were alive at the end of the period of observation as compared to those who had initially lost weight. Among our patients, the ones who were afebrile and were gaining weight, and in whom blood spitting was the immediate cause for the institution of pneumothorax, were the ones who did exceptionally well.

Chronic forms of pulmonary tuberculosis characterize essentially a productive type of disease while acute forms of tuberculosis characterize an exudative type of disease. When the results from pneumothorax treatment are correlated with the character of the underlying pathologic process, the foregoing observations receive basic substantiation. Alvermann (3) compared the results from pneumothorax in a group of patients who had predominantly productive pulmonary tuberculosis with a group of patients who had predominantly exudative pulmonary tuberculosis. The first group comprised 62 per cent able to work; 19 per cent unable to work and 19 per cent dead. The second group comprised 24 per cent able to work; 20 per cent unable to work and 56 per cent dead. In a similar analysis, Zinn (287), obtained durable results in 40 per cent of his patients with productive pulmonary tuberculosis in contrast to 13.5 per cent of his patients with exudative tuberculosis. Among Ahlenstiel's (2) patients who had sustained a satisfactory collapse of the lung, twice as many patients were able to work three years later who had initially productive disease as compared to those who had initially exudative disease. In other words, other factors being more or less equal, patients with a natural tendency towards healing do two or three times as well with pneumothorax as do patients who lack this tendency.

There are comparatively few patients with advanced pulmonary tuberculosis in need of pneumothorax treatment who fail to reveal roentgenologically, if not clinically, signs of involvement in the contralateral lung. In selected material, the contralateral lung is "essentially" free from disease in about one-third of instances. In unselected groups of patients, the incidence of contralateral involvement is much greater. In practice, however, one is less concerned with the presence of disease in the contralateral lung as with its character, extent, location and duration. We touched upon this phase of the problem elsewhere. The presence of tuberculous involvement in the "good" lung is naturally reflected in the results obtained. Burrell (47) found, eight years after the discontinuation of pneumothorax treatment, that in instances where the better lung had had active disease, a sixth of the patients obtained arrest of the disease. In instances where the better lung had been extensively involved, pneumothorax offered no real hope at all. Kendall and Ross (138), Trail and Stockman (269) and many others have likewise emphasized the importance of unilaterality of the disease in the obtainment of good results from pneumothorax treatment.

The most decisive single factor that determines success with pneumothorax treatment is the effectiveness of the collapse which the diseased lung sustains. The fact that good results may follow partial collapse of the lung and vice versa does not necessarily detract from the importance of this factor. It merely indicates that one is dealing with several elements, the chief one being the character of the disease itself. The term, "effective," obviously implies not only a mechanical component but a biological one as well. An effective pneumothorax presupposes the obliteration of tuberculous cavities and the transformation of caseous foci into fibrous tissue, the disappearance of tubercle bacilli from the sputum and the clinical rehabilitation of the patient.

When one compares the results from pneumothorax in patients who sustained an effective collapse of the lung with those who sustained an ineffective collapse, the difference, as shown in table 1, is very striking. Equally instructive are the results obtained in patients who sustained an ineffective collapse of the lung as compared with "con-

TABLE 1

Relation of character of collapse to results

SOURCE	CHARACTER OF COLLAPSE	NUMBER	RESULTS
Ahlenstiel (2)	Good pneumothorax	136	51.4% able to work
	Incomplete	166	25.4% able to work
	Unsuccessful	61	20.5% able to work
	Refused pneumothorax	104	22.5% able to work
Amberson (6)	Cavities closed	89	78 (87.6%) living
	Cavities not closed	76	35 (41.6%) living
Burrell (48)	Efficient	153	43 (28%) arrested
			7 (6%) alive but not arrested
			103 (67%) dead
	Partial and incomplete	29	3 (10%) arrested
			1 (4%) alive but not arrested
			25 (86%) dead
Cooper and Stallings (60) (unilateral disease)	Satisfactory	104	54 (52%) improved
			50 (48%) unimproved
	Unsatisfactory	78	22 (28%) improved
			56 (72%) unimproved
Gravesen (109)	Practicable	143	55 (38.5%) fit for work
			5 (3.5%) ill with tuberculosis
			83 (58%) dead
	Not practicable	73	9 (11.8%) fit for work
			3 (3.9%) ill with tuberculosis
			63 (81.8%) dead
			2 (2.6%) unknown
Kendall and Ross (138) (unilateral disease)	Satisfactory	143	91 (63.7%) improved, working or well
			52 (36.3%) unimproved or dead
	Unsatisfactory or not obtained	82	27 (33%) improved, working or well
			55 (67%) unimproved or dead
Macfie and Alexander (160)	Successful	166	94 (57%) alive
			72 (43%) dead
	Failed to induce	34	12 (38%) alive
			22 (62%) dead

TABLE 1—*Concluded*

SOURCE	CHARACTER OF COLLAPSE	NUMBER	RESULTS
Matson et al. (169)	Satisfactory	235	114 (48%) clinically well 44 (18%) arrested 52 (22%) dead
	Partial	245	28 (11%) clinically well 29 (12%) arrested 142 (58%) dead
	No free space	120	7 (5%) clinically well 11 (9%) arrested 80 (66%) dead
Peters, A. et al. (200)	Effective	151	142 (94%) living 9 (6%) dead
	Ineffective	245	146 (59.6%) living 99 (40.4%) dead
Peters, L. S. (204)	Good collapse	167	89 (53%) clinically well 41 (24%) dead
	Poor collapse	140	36 (25%) clinically well 63 (44%) dead
	No free space	120	20 (16%) clinically well 74 (60%) dead
Rist (219)	Successful	759	387 (52%) healed or clinically well 132 (17.5%) living 240 (30.5%) dead
	Unsuccessful	94	8 (8.5%) able to work 35 (37.2%) living 51 (54.2%) dead
	Refused pneumothorax	74	35 (47%) living 39 (53%) dead
Trail and Stockman (269)	Successful	91	60 (66%) tuberculosis negative or no sputum 16 (17%) tuberculosis positive 15 (16%) dead
	Unsuccessful	31	7 (22%) tuberculosis negative or no sputum 7 (22%) tuberculosis positive 17 (55%) dead

trol" groups of patients (those who refuse treatment and those in whom no free pleural space can be found). The statistics of Matson, Matson and Bisaillon (169), Rist (219) and Ahlenstiel (2) clearly indicate that a pneumothorax which is unsuccessful is no better than none at all. Indeed, considering the risks and inconveniences incurred, the latter is much the preferable. Obviously, a measure that does not bring about an effective collapse of the lung within a reasonable length of time had better be supplemented by another or substituted for another as early as possible.

The foregoing observations are best illustrated when applied to pneumothorax because this treatment lends itself to such comparisons. There is every reason to believe that the same applies to all collapse measures. One must conclude that a collapse measure that is not directed primarily towards the obliteration of tuberculous cavities or that does not serve as an adjunct to such an objective, is of doubtful value. The prime importance of the mechanical factor in pneumothorax treatment of pulmonary tuberculosis would seem, offhand, to support the belief of Riviere (220), Gillies (103) and others that the tuberculous lung should be collapsed as completely as possible to insure a favorable outcome. Yet, physicians who are impressed with the biological factors that underlie the healing of tuberculous cavities are content with a partial collapse of the lung providing cavity closure is realized. Modern "programs" of collapse therapy aim towards cavity closure by conservative means, if possible; by radical means, if necessary.

An important consideration in the evaluation of results from pneumothorax treatment, one that is often disregarded, is the interval that had been allowed to elapse between the time of discontinuation of refills and the assessment of the results. The immediate effects of collapsing a tuberculous lung are notably good. Unfortunately, the improvement is often symptomatic and temporary. With the passing months, the number of patients in whom the treatment continues to be successful steadily decreases and by the end of the first two years the picture is entirely changed. At the end of another two or three years the majority of the patients whose disease had not become arrested are dead and it is only then that the results begin to assume permanent form. They are fairly constant after a lapse of six or seven years. Since the greatest fluctuations occur within the first two years following the discontinuation of treatment, only an optimist reports results before allowing this minimum of time to elapse.

The greater the care exercised in the interpretation of two- or three-year results, the more durable will these turn out to be in later years. In March 1934, the writer (233) had occasion to report on the results from pneumothorax in 324 patients with pulmonary tuberculosis, of a total number of 377 who had been treated at the Montefiore Hospital and in its country sanatorium during the years 1916 to and including 1930. The results, which were rather poor, since the treatment in those years included a majority with advanced, bilateral tuberculosis, are given in table 2.

TABLE 2

Two- to fifteen-year end results in 324 cases, 1916–1930

CONDITIONS*	NUMBER		PREDOMINANTLY UNILATERAL PULMONARY TUBERCULOSIS		PREDOMINANTLY BILATERAL PULMONARY TUBERCULOSIS	
			Duration of pneumothorax			
			3 months or more	Less than 3 months	3 months or more	Less than 3 months
Clinically arrested	44		41	1	2	0
Sputum negative		35				
No sputum		5				
Sputum unknown		4				
Improved	23		19	0	4	0
Sputum negative		8				
Sputum positive		2				
No sputum		7				
Sputum unknown		6				
Stationary	18		14	2	0	2
Progressive	11		4	1	5	1
Uncertain	5		4	1	0	0
Dead†	186		61	42	31	52
Within 3 months of induction		30				
Within 6 months of induction		59				
Within 1 year of induction		88				
Within 2 years of induction		141				
Within 5 years of induction		174				
Total	318		143	47	42	55
*Bilateral pneumothorax, not analyzed	3					
†Non-tuberculous causes, not analyzed	3					
	324					

In the Spring of 1936, the writer reviewed the results in the group of 143 patients with predominantly unilateral pulmonary tuberculosis previously reported who had received pneumothorax for three months or longer. The revised 5- to 20-year end results are shown in table 3.

The results from pneumothorax treatment, as reported by 10 different observers, are given in table 4.

The results from pneumothorax treatment do not express the real value of the procedure if the indications that prompted its utilization are not taken into account. A measure may be successful insofar as it fulfills the physician's expectations, yet the value of the treatment may not find expression in the results obtained. One is apt to be disappointed if a measure does not do more than was expected of it. Harms and Grünswald (118) analyzed their results from pneumothorax in 800 patients with respect to the indications for which the treatment was originally instituted. In approximately 30 per cent of their patients the indications were absolute or relative, the former referring to instances of unilateral, fibroulcerative disease, and the latter to instances with fibrotic infiltrations in the contralateral lung. The indications in the remaining 70 per cent, with few exceptions, were of a symptomatic nature. Of the patients who were later found able to work, 80 per cent had met initially either absolute or relative indications while 44 per cent had met purely symptomatic or other vital indications.

TABLE 3

Five- to twenty-year end results, in 143 patients, with predominantly unilateral pulmonary tuberculosis, treated by pneumothorax for three months or longer, 1916–1930. Condition of patients in 1936

	NUMBER OF CASES
Clinically arrested	43
Improved	6
Progressive	6
Exact status not ascertainable	7
Dead	70
Not traced	11
Total	143

TABLE 4

Comparative results from induced pneumothorax in 1926 cases, reported by 10 different observers

SOURCE	TYPE OF MATERIAL	PERIOD OF OBSERVATION	NUMBER	LIVING	PER CENT	DEAD	PER CENT	RESULTS OF TOTAL NUMBER
		years						
Münchbach (185)		2–9	475	273	57	202	43	Fully able to work, 37 per cent
Gravesen (109)	Pneumothorax practicable	2–12	140	60	43	80	57	Able to work, 39 per cent
Roloff (222)	Simple unilateral pneumothorax, 6 months or longer	2–12	262	*	60	*	40	Sputum negative, 45 per cent
Maendl (164)		2–12	172	85	49	87	51	Fully able to work, 36 per cent
Peters (199)	Satisfactory or incomplete effective collapse; exclusive of those under treatment	2–14	167	79	47	88	53	Condition satisfactory, 30 per cent
Arni (14)	Successful pneumothorax	2–14	170	46	27	124	73	Fully able to work, 21 per cent
Zinn and Siebert (288)	Partial or total pneumothorax	$2\frac{1}{2}$–15	183	77	42	106	58	Healed, 15 per cent
Hurrell (128)	Successful pneumothorax induced	3–10	99	27	27	72	72	Well, 17 per cent
Schröder (241)	Average duration of pneumothorax, $8\frac{1}{4}$ months	3–15	115	50	44	65	56	Healed, 37 per cent
Rubin (233)	Predominantly unilateral; pneumothorax 3 months or more	2–15	143	82	57	61	43	Clinically arrested, 29 per cent; sputum negative, 30 per cent
Total..........	More or less pneumothorax induced	*	1926	779	47	885	53	

Any discussion of treatment of pulmonary tuberculosis would be incomplete did it fail to touch on the significance of after-cure in securing permanent results. The subject has been the theme of countless symposia and a voluminous literature. The problem is intimately associated with social and economic factors that cannot be dwelt upon here. The major topics of such discussions deal with the necessity of sheltered employment, medical supervision and, when needed, the extension of financial help to the patient's family. Public health and social workers are unanimous in the belief that an adequate program of after-care, when the individual resumes his place in the community, is the greatest bulwark against relapse.

From a purely medical point of view, however, in reflecting on the number of tuberculosis patients whose disease had become arrested and who had suffered a relapse, one is hard pressed to correlate the adequacy of the after-care with the occurrence of relapse. Stimulated by the incisive views of Dr. Wessler on the subject, the writer has been lately paying particular attention to the patients in the follow-up clinic of the Montefiore Hospital who suffer relapse. Almost without exception it seems that patients who need rehospitalization did not have their disease under arrest in the first place. In the instances where the breakdown occurred in patients with supposedly arrested disease, relapse occurred in most instances within a year or two following discharge from the sanatorium or the hospital, suggestive that possibly the physician's interpretation of the patient's status may have been incorrect. The quality of the after-care, incidentally, is apt to be of an unusually high order during the first year or two after discharge from active treatment.

The majority of the patients attending the Montefiore Tuberculosis Clinic suffer the same hardships as do patients in other "free" clinics. They have to skimp to make ends meet on the meager allowance which they receive from welfare agencies. To many the price of the carfare to the clinic is an important item. Not infrequently an individual with healed pulmonary tuberculosis expresses disappointment when told that no evidence of activity is demonstrable in the lungs. A relapse would make him eligible for rehospitalization and this in turn would qualify his family for additional support. Obviously, it is not our intention to minimize the importance of after-care that concerns itself with helping the individual adjust himself economically in the community. The writer simply draws attention to the fact that the quality of the after-care is not a significant element in causing relapse in instances of arrested pulmonary tuberculosis. The supervision of patients whose disease, on discharge from an institution, is in a state of quiescence is essentially a continuation, at home, of the rest treatment begun in the sanatorium or the hospital. It is not after-care. One must conclude that the results from treatment of pulmonary tuberculosis do not depend on the quality of the after-care but on the quality of the initial treatment which the patient receives.

Our interpretation of the significance of after-care in insuring results from treatment received corroboration in remarks made by Hochhauser (126), executive director of the Altro Shops, an organization that employs sanatorium graduates many of whom are under the medical supervision of the writer. In an address at a meeting of the National Tuberculosis Association, in 1933, he states: "Since 1929 we have been anticipating an increase both in number of new cases of tuberculosis and in reactivation among our arrested cases who have returned to work. For instance, there are a number of our workshops graduates (Altro Work Shops, New York City) who had lost their jobs in industry and were again compelled to apply for charitable aid. Conditions that gave others heartaches or headaches, gave them chest aches. When called for routine examinations they often complained of symptoms they thought were indicative of a relapse, but careful observation and examination failed to show pulmonary reactivation."

The implantation and spread of tuberculosis in a community, as in the individual afflicted, involves two elements, aptly termed by Osler, "seed" and "soil." The catalyzer is the great unknown. There are specific groups in the community, just as there are specific organs in the body, that offer exceptionally receptive soil for the growth of the tubercle bacillus and unusual opportunities for its dissemination. The adolescent boy or girl, the man working in an atmosphere of silica dust, the Negro, among other groups, constitute fertile soil. The elderly, "bronchitic" folks at home with dormant tuberculosis in the lungs, the many individuals with undiagnosed, active tuberculosis, the many others known to have tuberculosis but waiting months for a hospital bed to become available, all constitute inexhaustible seed-bags.

To what extent can the principles that guide the treatment of tuberculosis in the individual be applied to the community at large?

To what extent can the ubiquitous seeding of the tubercle bacillus be restricted by applying a measure such as pneumothorax?

The increasing number of patients being treated by collapse measures bring these problems to the fore with increasing force.

The principles that guide one's efforts in the treatment of clinical tuberculosis involve primarily the eradication of the source of tubercle bacilli. By this means one protects the uninvolved parts of the affected organ and the body as a whole against the spread of the disease. Tubercle bacilli surrounded by a firm fibrotic capsule are of no danger to the life of the individual, as witness the large number of individuals infected but not diseased. It is the constant passage of tubercle bacilli through natural ducts or by way of the blood stream that ultimately kills the patient. Modern treatment of pulmonary tuberculosis aims towards the encompassment of the disease process within narrow limits and its ultimate conversion into scar tissue so as to close all communications between the source of the tubercle bacilli and the outside.

An individual with active pulmonary tuberculosis may be likened to a "caseous focus" in the community. The incidence of infection and disease in a community is in direct ratio to the number of such "caseous foci" at large. It would seem, as a public health measure, that the eradication of tuberculosis is largely a matter of segregation of the diseased members of the community. As a corollary, therefore, it would be logical to assume that extensive use of collapse treatment would indirectly serve the same purpose.

A critical analysis of the situation, however, convinces the writer that, in the utilization of collapse treatment of pulmonary tuberculosis, the less one stresses the public health aspects and the more one stresses the individual problems involved, the better will be the results both from the public and individual standpoint. Facilities for the immediate hospitalization of the tuberculous should be available to insure adequate treatment of the afflicted and to minimize the danger of massive and repeated infection in the patient's home. In the utilization of the various collapse measures, however, epidemiological considerations, in their broader phases, should play a secondary rôle.

Experience has shown that by the time tuberculosis is diagnosed it is usually in an advanced stage and had been present in the individual for a considerable time during which he had come in contact with countless others. It is a well established fact that for every death from tuberculosis, there is a variable number of individuals with unrecognized, active disease at large in the community. Of those who enter modern tuberculosis institutions, 25 per cent, on the average, receive some form of collapse treatment. Of those in whom the treatment is applied, approximately a third receive lasting benefit. Obviously, the collapse treatment of pulmonary tuberculosis cannot influence greatly the morbidity or the mortality rates from the disease.

In a careful analysis Drolet (74) has recently shown that the fatality rate from tuberculosis (number of deaths per number of admissions), in 40 Metropolitan New York institutions, with an increasing percentage of patients receiving collapse treatment, has remained practically the same during the past ten years, 24 per cent in 1927; 21 per cent in 1936. The recent reports from England by Hartley, Wingfield and Burrows (119), Stockman and associates (257), and Bentley (23) give convincing proof to the effect that modern methods of treatment of pulmonary tuberculosis as yet "affect the individual only and only then if he be lucky enough to fall into a certain selected category. The bulk of the patients presenting themselves for treatment do not, however, fall into this selected category" (119).

The foregoing considerations are raised because there is a distinct danger that mass treatment of pulmonary tuberculosis by collapse measures may impair the quality of the treatment to a harmful degree. In the treatment of pulmonary tuberculosis by collapse measures, the welfare of the individual is paramount to the welfare of the public. Any benefit accruing to the latter is in the nature of a by-product depending on the quality of care which the individual receives. The public health is best served by early diagnosis of the disease and hospitalization of the sick; the patient's health is best served by individualization of treatment.

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